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#### (54) Title: GENES ESSENTIAL FOR MICROBIAL PROLIFERATION AND ANTISENSE THERETO

(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms as well as to screen for antimicrobial agents.

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#### GENES ESSENTIAL FOR MICROBIAL PROLIFERATION AND ANTISENSE THERETO

#### **BACKGROUND OF THE INVENTION**

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited. Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common Staphylococcus aureus (staph). This organism is commonly found in our environment and is responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by stubborn strains of bacteria, like staph. In short, the bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

There are a number of causes for the predicament in which practitioners of medical arts find themselves. Over-prescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patient is also partly responsible, for even in instances where an antibiotic is the appropriate treatment, patients will often improperly use the drug, the result being yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial scourges that have haunted humanity remain, in spite of the development of modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now advancing on the health of humanity. A new generation of antibiotics to once again deal with the pending health threat that bacteria present is required.

#### **Discovery of New Antibiotics**

As more and more bacterial strains become resistant to the panel of available antibiotics, new compounds are required. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug is nearly US \$500 million, and the

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average time is 15 years from laboratory to patient. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of an organism make for excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the organism. Once a target is identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Using physical and computational techniques, to analyze structural and biochemical targets in order to derive compounds that interact with a target is called rational drug design and offers great future potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

Escherichia coli represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6 x 10<sup>6</sup> base pairs of the Escherichia coli (E. coli) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire E. coli genome has been sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the metB-malB Region of Escherichia coli K12, 1975, J. Bacteriol. 126: 48-55).

Novel, safe and effective antimicrobial compounds are needed in view of the rapid rise of antibiotic resistant microorganisms. However, prior to this invention, the characterization of even a single bacterial gene was a painstaking process, requiring years of effort. Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that

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encode gene products required for proliferation and for methods to identify molecules that interact with and alter the functions of such genes and gene products.

#### **SUMMARY OF THE INVENTION**

One embodiment of the present invention is a purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 1-127, wherein expression of said nucleic acid inhibits proliferation of a microorganism. The nucleic acid sequence may be complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a microorganism. The nucleic acid sequence may be complementary to at least a portion of an RNA required for proliferation of a microorganism. The RNA may be an RNA encoding more than one gene product.

Another embodiment of the present invention is a nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-127, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive bases of one of SEQ ID NOs: 1-127.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid sequences of each of the preceding paragraphs. The promoter may be active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a host cell containing the vectors of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 128-298.

Another embodiment of the present invention is a fragment of the nucleic acid of the preceding paragraph, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 128-298.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid of the preceding two paragraphs.

Another embodiment of the present invention is a purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding

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region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-127, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127, the sequences complementary to SEQ ID NOs.: 1-127 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127 as determined using BLASTN version 2.0 with the default parameters. The nucleic acid may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Staphylococcus aureus, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127. The polypeptide may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-469.

Another embodiment of the present invention is a host cell containing the vector of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides. The polypeptide may comprise a polypeptide comprising one of SEQ ID NOs.: 299-469 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least

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50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127 as determined using FASTA version 3.0t78 with the default parameters. The polypeptide may have at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-469 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-469 as determined using FASTA version 3.0t78 with the default parameters.

Another embodiment of the present invention is an antibody capable of specifically binding one of the polypeptides of the preceding paragraph.

Another embodiment of the present invention is a method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 into a cell. The method may further comprise the step of isolating said polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting said gene product with a candidate compound and determining whether said compound influences the activity of said gene product. The gene product may be a polypeptide and said activity may be an enzymatic activity. The gene product may be a polypeptide and said activity may be a carbon compound catabolism activity. The gene product may be a polypeptide and said activity may be a transporter activity. The gene product may be a polypeptide and said activity may be a transcriptional activity. The gene product may be a polypeptide and said activity may be a DNA replication activity. The gene product may be a polypeptide and said activity my be a cell division activity. The gene product may be a polypeptide and said activity my be a cell division activity. The gene product may be a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

AThe method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

- (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
  - (b) contacting said target with a candidate compound or nucleic acid; and
  - (c) measuring an activity of said target.

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The target may be a messenger RNA molecule and said activity may be translation of said messenger RNA. The target may be a messenger RNA molecule and said activity may be transcription of a gene encoding said messenger RNA. The target may be a gene and said activity may be transcription of said gene. The target may be a nontranslated RNA and said activity may be processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex. The target gene or RNA may encode a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound or nucleic acid identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising the steps of:

- (a) expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;
  - (b) contacting said sensitized cell with a compound; and
  - (c) determining whether said compound inhibits the growth of said sensitized cell.

The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The cell may be an E. coli cell. The cell may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae,

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Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level. Growth inhibition may be measured by monitoring optical density of a culture growth solution. The gene product may be a polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-469. The gene product may be an RNA.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a compound with activity against the product of said gene into a population of cells expressing said gene. The compound may be an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof. The proliferation inhibiting portion of one of SEQ ID NOs.: 1-127 may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive bases of one of SEQ ID NOs.: 1-127. The population may be a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The population may be a population of Gram negative bacteria. The population may be a population of E. coli cells. The population may be a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis cells or cells from any species falling within the genera of any of the above species. The gene may encode a polypeptide comprising a sequence selected from the group consisting of SEO ID NOs.: 299-469.

Another embodiment of the present invention is a preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof in a pharmaceutically

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acceptable carrier. The proliferation-inhibiting portion of one of SEQ ID NOs.: 1-127 may comprise at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon. The antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a proliferation inhibiting portion thereof.

The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population. The cell may be contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid. The cell may be contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a ribozyme into said cellpopulation, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide. The cell may be contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell. The cell may be contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid. The antisense nucleic acid may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127. The antisense nucleic acid may be an oligonucleotide.

Another embodiment of the present invention is a method for identifying a gene which is required for proliferation of a microorganism comprising:

- (a) contacting a microorganism other than E. coli with a nucleic acid selected from the group consisting of SEO ID NOs.: 1-127;
- (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
- (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.

  The microorganism may be a Gram negative bacterium. The microorganism may be selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus

neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The method may further comprise introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.

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Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:

- (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127;
- (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
- (c) contacting said first microorganism with a sublethal level of said inhibitory nucleic acid, thus sensitizing said first microorganism;
  - (d) contacting the sensitized microorganism of step (c) with a compound; and
- (e) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism. Step (a) may comprise identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEO ID NOs. 1-127 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database. Step (a) may comprise identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene. Step (a) may comprise expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 in said microorganism. The inhibitory nucleic acid may be an antisense nucleic acid. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of said homolog. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of the operon encoding said homolog. The step of contacting the first microorganism with a sublethal

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level of said inhibitory nucleic acid may comprise directly contacting said microorganism with said inhibitory nucleic acid. The step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid may comprise expressing an antisense nucleic acid to said homolog in said microorganism. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method of identifying a compound having the ability to inhibit proliferation comprising:

- (a) contacting a microorganism other than *E. coli* with a sublethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
  - (b) contacting the sensitized microorganism of step (a) with a compound; and
- (c) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having activity against a biological pathway required for proliferation comprising:

- (a) sensitizing a cell by expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, in said cell to reduce the activity or amount of said gene product;
  - (b) contacting the sensitized cell with a compound; and
  - (c) determining whether said compound inhibits the growth of said sensitized cell.
- The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The Gram negative bacterium may be E. coli. The cell may be selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae,

Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level. The inhibition of proliferation may be measured by monitoring the optical density of a liquid culture. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit cellular proliferation comprising:

- (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127;
  - (b) contacting said cell with a compound; and

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(c) determining whether said compound reduces proliferation of said contacted cell. The determining step may comprise determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise an antisense nucleic acid to a gene or operon required for proliferation. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise a compound known to inhibit growth or proliferation of a microorganism. The cell may contain a mutation which reduces the activity or level of said gene product required for proliferation of said cell. The mutation may be a temperature sensitive mutation. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

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(a) expressing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;

- (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
- (c) determining whether said cell is sensitive to said compound.

  The determining step may comprise determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid and wherein said gene or gene product lies in the same pathway on which said compound acts if said cell expressing said sublethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sublethal level of said antisense nucleic acid.

The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method for determining the biological pathway on which a test compound acts comprising:

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- (a) expressing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
  - (b) contacting said cell with said test compound; and
  - (c) determining whether said cell is sensitive to said test compound.

The determining step may comprise determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid. The method may further comprise:

- (d) expressing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and
- (e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.

Another embodiment of the present invention is a compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.

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Another embodiment of the present invention is a method for manufacturing an antibiotic comprising the steps of screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and manufacturing the compound so identified.

The screening step may comprise performing any one of the methods of identifying a compound described above.

Another embodiment of the present invention is a method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 to said subject. The method of subject may be selected from the group consisting of vertebrates, mammals, avians, and human beings. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli* ribosomal protein rplW (AS-rplW) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the elaD gene (AS-elaD) which is not known to be involved in protein synthesis and which is also essential for proliferation.

Figure 2A is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to rplW gene (AS-rplW) carried out in the presence of 0, 20 or 50 µM IPTG.

Figure 2B is a tetracycline dose response curve in E. coli transformed with an IPTG-inducible plasmid containing antisense to elaD gene (AS-elaD) carried out in the presence of 0, 20 or 50  $\mu$ M IPTG.

Figure 3 is a graph showing the fold increase in tetracycline sensitivity of E. coli transfected with antisense clones to essential ribosomal protein genes L23 (AS-rpIW) and L7/L12

and L10 (AS-rplLrplJ). Antisense clones to genes known not to be involved in protein synthesis (atpB/E(AS-atpB/E), visC (AS-visC, elaD (AS-elaD), yohH (AS-yohH) are much less sensitive to tetracycline.

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#### **Definitions**

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as cell walls. Biological pathways that are usually required for proliferation of microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

By "inhibit activity of a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene or to reduce the level or activity of a product of the gene. Agents which inhibit the activity of a gene include agents that inhibit transcription of the gene, agents that inhibit processing of the transcript of the gene, agents that reduce the stability of the transcript of the gene, and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which inhibit the activity of a gene can act to decrease expression of the operon in which the gene resides or alter the folding or processing of operon RNA so as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as ribosomal RNA, a translated RNA (mRNA) or the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are antisense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell.

By "activity against a nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell.

By "activity against a gene" is meant having the ability to inhibit the function or expression of the gene in a cell.

By "activity against an operon" is meant having the ability to inhibit the function or reduce the level of one or more products of the operon in a cell.

By "antibiotic" is meant an agent which inhibits the proliferation of a microorganism.

By "identifying a compound" is meant to screen one or more compounds in a collection of compounds such as a combinatorial chemical library or other library of chemical compounds or to characterize a single compound by testing the compound in a given assay and determining whether it exhibits the desired activity.

By "inducer" is meant an agent or solution which, when placed in contact with a microorganism, increases transcription from a desired promoter.

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As used herein, "nucleic acid" means DNA or RNA. Thus, the terminology "the nucleic acid of SEQ ID NO: X" includes both the DNA sequence of SEQ ID NO: X and an RNA sequence in which the thymidines in the DNA sequence have been substituted with uridines in the RNA sequence and in which the deoxyribose backbone of the DNA sequence has been substituted with a ribose backbone in the RNA sequence.

As used herein, "sublethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

#### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention describes a group of E. coli genes and gene families required for growth and/or proliferation. A proliferation-required gene or gene family is one where, in the absence of a gene transcript and/or gene product, growth or viability of the microorganism is reduced or eliminated. Thus, as used herein the terminology "proliferation-required" or "required for proliferation" encompasses sequences where the absence of a gene transcript and/or gene product completely eliminates cell growth as well as sequences where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses novel assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds. The present invention also describes methods for identification of homologous genes in organisms other than E. coli.

The present invention utilizes a novel method to identify proliferation-required *E. coli* sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted into an inducible expression vector, thus forming an expression library. Although the insert nucleic acids may be derived from the chromosome of the organism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term expression is defined as the production of an RNA molecule from a gene, gene fragment, genomic

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fragment, or operon. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into an *E. coli* population to search for genes that are required for bacterial proliferation. Because the library molecules are foreign to the population of *E. coli*, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

Expression of the exogenous nucleic acid fragments in the test population of *E. coli* containing the expression vector library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid sequences carried by the expression vector library. The test population of *E. coli* cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that, upon activation and expression, negatively impact the growth of the *E. coli* screen population were identified, isolated, and purified for further study.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in *E. coli* cultures expressing exogenous nucleic acid sequences and growth in cultures not expressing these sequences is compared. Growth measurements are assayed by examining the extent of growth by measuring optical densities. Alternatively, enzymatic assays can be used to measure bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that failed to grow or grow with reduced efficiency under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acid sequences of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleic acid sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a sequence of interest is sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleic acid sequence.

Determination of sequence source is achieved by comparing the obtained sequence data with known sequences in various genetic databases. The sequences identified are used to probe these gene databases. The result of this procedure is a list of exogenous nucleic acid sequences corresponding to a list that includeds novel bacterial genes required for proliferation as well as genes previously identified as required for proliferation.

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The number of DNA and protein sequences available in database systems has been growing exponentially for years. For example, at the end of 1998, the complete sequences of *Caenorhabditis elegans*, *Saccharomyces cerevisiae* and nineteen bacterial genomes, including *E. coli* were available. This sequence information is stored in a number of databanks, such as GenBank (the National Center for Biotechnology Information (NCBI), and is publicly available for searching.

A variety of computer programs are available to assist in the analysis of the sequences stored within these databases. FastA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63-98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl. Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleic acid sequences.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance in using the program can be obtained by e-mail at <a href="mailto:blast@ncbi.nlm.nih.gov.">blast@ncbi.nlm.nih.gov.</a>.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences. The genes of an operon are co-transcribed and are often related functionally. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid sequence corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation. Accordingly, determining which of the genes that are encoded within the operons are individually required for proliferation is often desirable.

In one embodiment of the present invention, an operon is dissected to determine which gene or genes are required for proliferation. For example, the RegulonDB DataBase described by Huerta et al. (Nucl. Acids Res. 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational\_Biology/regulondb/, may be used. to identify the boundaries of operons encoded within microbial genomes. A number of techniques that are well known in the art can be used to dissect the operon. In one aspect of this embodiment, gene disruption by homologous recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of homologous recombination. The method described by Link et al. (J. Bacteriol 1997 179:6228) serves as an excellent example of these methods as applicable to disruption of genes in *E. coli*. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that sequences adjacent to the wild type gene (ca. 500 bp) are retained. These homologous sequences surrounding the deletion null allele provide targets for homologous recombination so that the wild type gene on the *E. coli* chromosome can be replaced by the constructed null allele.

The crossover PCR amplification product is subcloned into the vector pKO3, the features of which include a chloramphenicol resistance gene, the counter-selectable marker sacB, and a temperature sensitive autonomous replication function. Following transformation of an E. coli cell population with such a vector, selection for cells that have undergone homologous recombination of the vector into the chromosome is achieved by growth on chloramphenicol at the non-permissive temperature of 43°C. Under these conditions, autonomous replication of the plasmid cannot occur and cell are resistant to chloramphinicol only if the chloramphenicol resistance gene has been integrated into the chromosome. Usually a single crossover event is responsible for this integration event such that the E. coli chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence.

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This new *E. coli* strain containing the tandem duplication can be maintained at permissive temperatures in the presence of drug selection (chloramphenicol). Subsequently, cells of this new strain are cultured at the permissive temperature 30°C without drug selection. Under these conditions, the chromosome of some of the cells within the population will have undergone an internal homologous recombination event resulting in removal of the plasmid sequences. Subsequent culturing of the strain in growth medium lacking chloramphenicol but containing sucrose is used to select for such recombinative resolutions. In the presence of the counter-selectable marker *sacB*, sucrose is rendered into a toxic metabolite. Thus, cells that survive this counter-selection have lost both the plasmid sequences from the chromosome and the autonomously replicating plasmid that results as a byproduct of recombinative resolution.

There are two possible outcomes of the above recombinative resolution via homologous recombination. Either the wild type copy of the targeted gene is retained on the chromosome or the mutated null allele is retained on the chromosome. In the case of an essential gene, a single copy of the null allele would be lethal and such cells should not be obtained by the above procedure when applied to essential genes. In the case of a non-essential gene, roughly equal numbers of cells containing null alleles and cells containing wild type alleles should be obtained. Thus, the method serves as a test for essentiality of the targeted gene: when applied to essential genes, only cells with a wild type allele on the chromosome will be obtained.

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Other techniques have also been described for the creation of disruption mutations in *E. coli*. For example, Link et al. also describe inserting an in-frame sequence tag concommitantly with an in-frame deletion in order to simplify analysis of recombinants obtained. Further, Link et al. describe disruption of genes with a drug resistance marker such as a kanamycin resistance gene. Arigoni et al., (Arigoni, F. et al. A Genome-based Approach for the Identification of Essential Bacterial Genes, Nature Biotechnology 16: 851-856) describe the use of gene disruption combined with engineering a second copy of a test gene such that the expression of the gene is regulated by and inducible promoter such as the arabinose promoter to test the essentiality of the gene. Many of these techniques result in the insertion of large fragments of DNA into the gene of interest, such as a drug selection marker. An advantage of the technique described by Link et al. is that it does not rely on an insertion into the gene to cause a functional defect, but rather results in the precise removal of the coding region. This insures the lack of polar effects on the expression of genes downstream from the target gene.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene identified as required for proliferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the sequences encoding a signal peptide to facilitate secretion of the expressed protein.

Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 75, or more than 75 consecutive amino acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain sequences upstream and downstream of the coding sequence.

When expressing the coding sequence of an entire gene identified as required for bacterial proliferation or a fragment thereof, the nucleic acid sequence to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767. Fusion protein expression systems are also contemplated by the present invention.

Following expression of the protein encoded by the identified exogenous nucleic acid sequence, the protein is purified. Protein purification techniques are well known in the art. Proteins

encoded and expressed from identified exogenous nucleic acid sequences can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Chromatographic methods usable with the present invention can include ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography. Electrophoretic methods such one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising antibody columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene coding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the identified exogenous nucleic acid sequences. Both monoclonal and polyclonal antibodies can be generated against the expressed proteins. Methods for generating monoclonal and polyclonal antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

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Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene sequence is contemplated by the present invention.

The present invention further contemplates utility against a variety of other pathogenic organisms in addition to *E. coli*. For example, the invention has utility in identifying genes required for proliferation in prokaryotes and eukaryotes. For example, the invention has utility with protists, such as *Plasmodium* spp.; plants; animals, such as *Entamoeba* spp. and *Contracaecum* spp.; and fungi including *Candida* spp., (e.g., *Candida albicans*), *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*. In one embodiment of the present invention, monera, specifically bacteria are probed in search of novel gene sequences required for proliferation. This embodiment is particularly important given the rise of drug resistant bacteria.

The numbers of bacterial species that are becoming resistant to existing antibiotics are growing. A partial list of these organisms includes: Staphylococcus spp., such as S. aureus; Enterococcus spp., such as E. faecalis; Pseudomonas spp., such as P. aeruginosa, Clostridium spp., such as C. botulinum, Haemophilus spp., such as H. influenzae, Enterobacter spp., such as E. cloacae, Vibrio spp., such as V. cholera; Moraxala spp., such as M. catarrhalis; Streptococcus spp., such as S. pneumoniae, Neisseria spp., such as N. gonorrhoeae; Mycoplasma spp., such as

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Mycoplasma pneumoniae; Salmonella typhimurium; Helicobacter pylori; Escherichia coli; and Mycobacterium tuberculosis. The sequences identified as required for proliferation in the present invention can be used to probe these and other organisms to identify homologous required proliferation genes contained therein.

In one embodiment of the present invention, the nucleic acid sequences disclosed herein are used to screen genomic libraries generated from bacterial species of interest other than E. coli. For example, the genomic library may be from Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. Standard molecular biology techniques are used to generate genomic libraries from various microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences. The homologous sequences identified can then be used as targets for the identification of new, antimicrobial compounds with activity against more than one organism.

For example, the preceding methods may be used to isolate nucleic acids having a sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% identity to a nucleic acid sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-127, 128-298, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive bases thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)). For example, the homologous polynucleotides may have a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of SEQ ID NOs: 1-127, 128-298 or the sequences complementary thereto.

Additionally, the above procedures may be used to isolate nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, or at least 40% identity or similarity to a polypeptide having the sequence of one of SEQ ID NOs: 299-469or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78

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algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Alschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)).

Alternatively, homologous nucleic acids or polypeptides may be identified by searching a database to identify sequences having a desired level of homology to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids or polypeptides having at least 97%, at least 95%, at least 95%, at least 85%, at least 80%, at least 70%, at least 60%, or at least 50%, at least 40% identity or similarity to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid involved in proliferation. For example, the database may be screened to identify nucleic acids homologous to one of SEQ ID Nos. 1-127, 128-298 or polypeptides homologous to SEQ ID NOs. 299-469. In some embodiments, the database may be screened to identify homologous nucleic acids or polypeptides from organisms other than E. coli, including organisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species.

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrane, or the like. Such arrays can be used by researchers to quantify relative gene expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5807522.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays from Genosys consist of 12 x 24 cm nylon filters containing PCR products corresponding to 4290 ORFs from *E. coli*. 10 ngs of each are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done by phosphorimager.

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Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid against a proliferation-required gene. Analysis of the expression pattern indicated by hybridization to the array provides information on whether or not the target gene of the antisense nucleic acid is being affected by antisense induction, how quickly the antisense is affecting the target gene, and for later timepoints, what other genes are affected by antisense expression. For example, if the antisense is directed against a gene for ribosomal protein L7/L12 in the 50S subunit, its targeted mRNA may disappear first and then other mRNAs may be observed to increase, decrease or stay the same. Similarly, if the antisense is directed against a different 50S subunit ribosomal protein mRNA (e.g. L25), that mRNA may disappear first followed by changes in mRNA expression that are similar to those seen with the L7/L12 antisense expression. Thus, the mRNA expression pattern observed with an antinsense nucleic acid against a proliferation required gene may identify other proliferation-required nucleic acids in the same pathway as the target of the antisense nucleic acid. In addition, the mRNA expression patterns observed with candidate drug compounds may be compared to those observed with antisense nucleic acids against a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of candidate drug compounds for use in screening methods such as those described below.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different organisms, gene expression arrays can identify homologous genes in the two organisms.

The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In this embodiment, the conserved portions of sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene is expressed in an autologous organism or

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in a heterologous organism in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologus organism. In still another aspect of this embodiment, the homologous gene or portion is expressed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous organism.

The homologous sequences to proliferation-required genes identified using the techniques described herein may be used to identify proliferation-required genes of organisms other than *E. coli*, to inhibit the proliferation of organisms other than *E. coli* by inhibiting the activity or reducing the amount of the identified homologous nucleic acid or polypeptide in the organism other than *E. coli*, or to identify compounds which inhibit the growth of organisms other than *E. coli* as described below.

In another embodiment of the present invention, *E. coli* sequences identified as required for proliferation are transferred to expression vectors capable of function within non-*E coli* species. As would be appreciated by one of ordinary skill in the art, expression vectors must contain certain elements that are species specific. These elements can include promoter sequences, operator sequences, repressor genes, origins of replication, ribosomal binding sequences, termination sequences, and others. To use the identified exogenous sequences of the present invention, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into an expression vector adapted for use in the species of bacteria to be screened.

Expression vectors for a variety of other species are known in the art. For example, Cao et al. report the expression of steroid receptor fragments in *Staphylococcus aureus*. J. Steroid Biochem Mol Biol. 44(1):1-11 (1993). Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: *Salmonella typhimurium*, *Pseudomonas putida*, and *Pseudomonas aeruginosa*. J. Bacteriol. 172(8):4448-55 (1990). These examples demonstrate the existence of molecular biology techniques capable of constructing expression vectors for the species of bacteria of interest to the present invention.

Following the subcloning of the identified nucleic acid sequences into an expression vector functional in the microorganism of interest, the identified nucleic acid sequences are conditionally transcribed to assay for bacterial growth inhibition. Those expression vectors found to contain sequences that, when transcribed, inhibit bacterial growth are compared to the known genomic sequence of the pathogenic microorganism being screened or, if the homologous sequence from the organism being screened is not known, it may be identified and isolated by hybridization to the proliferation-required *E. coli* sequence interest or by amplification using primers based on the proliferation-required *E. coli* sequence of interest as described above.

The antisense sequences from the second organism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, and introduced into the

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second organism. The techniques described herein for identifying *E. coli* genes required for proliferation may thus be employed to determine whether the identified sequences from a second organism inhibit the proliferation of the second organism.

Antisense nucleic acids required for the proliferation of organisms other than E. coli or the genes corresponding thereto, may also be hybridized to a microarray containing the E. coli ORFs to gauge the homology between the E. coli sequences and the proliferation-required nucleic acids from other organisms. For example, the proliferation-required nucleic acid may be from Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni or Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. The proliferation-required nucleic acids from an organism other than E. coli may be hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the sequence on the microarray. This would provide an indication of homology across the organisms as well as clues to other possible essential genes in these organisms.

In still another embodiment, the exogenous nucleic acid sequences of the present invention that are identified as required for bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be directed against the proliferation-required genes whose sequence corresponds to the exogenous nucleic acid probes identified here (i.e. the antisense nucleic acid may hybridize to the gene or a portion thereof). Alternatively, antisense therapeutics can be directed against operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to any gene in the operon in which the proliferation-required genes reside). Further, antisense therapeutics can be directed against a proliferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acid sequences complementary to sequences required for proliferation as diagnostic tools. For example, nucleic acid probes complementary to proliferation-required sequences that are specific for particular species of microorganisms can be used as probes to identify particular microorganism species in clinical specimens. This utility provides a rapid and dependable method by which to identify

the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to prescribe species specific antimicrobial compounds to treat such infections. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences can also be used to screen for specific microorganisms that produce such proteins in a species-specific manner.

The following examples teach the genes of the present invention and a subset of uses for the *E. coli* genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

#### **EXAMPLES**

The following examples are directed to the identification and exploitation of *E. coli* genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences.

#### Genes Identified as Required for Proliferation of E. coli

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Exogenous nucleic acid sequences were cloned into an inducible expression vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of exogenous nucleic acid sequences cloned into the IPTG-inducible expression vector pLex5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)). Upon activation or induction, the expression vectors produced an RNA molecule corresponding to the subcloned exogenous nucleic acid sequences. The RNA product was in an antisense orientation with respect to the *E. coli* genes from which it was originally derived. This antisense RNA then interacted with sense mRNA produced from various *E. coli* genes and interfered with or inhibited the translation of the sense messenger RNA (mRNA) thus preventing protein production from these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for the proliferation, bacterial cells containing an activated expression vector failed to grow or grew at a substantially reduced rate. Similar results have also be obtained in cases where the gene encodes a non-translated RNA, such as a ribosomal RNA.

#### **EXAMPLE 1**

#### Inhibition of Bacterial Proliferation after IPTG induction

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the  $OD_{450}$  every 30 minutes (min). To study the effects of transcriptional induction on solid medium,  $10^2$ ,  $10^3$ ,  $10^4$ ,  $10^5$ ,  $10^6$ ,  $10^7$  and  $10^8$  fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3  $\mu$ l of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as containing a sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid

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sequence corresponds, or a gene within the operon containing the inserted nucleic acid, may be required for proliferation in *E. coli*.

#### Characterization of Isolated Clones Negatively Affecting E. coli Proliferation

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Following the identification of those expression vectors that, upon expression, negatively impacted *E. coli* growth or proliferation, the inserts or nucleic acid fragments contained in those expression vectors were isolated for subsequent characterization. Inserts in expression vectors of interest were subjected to nucleic acid sequence determination.

#### **EXAMPLE 2**

# Nucleic Acid Sequence Determination of Identified Clones Expressing Nucleic Acid Fragments with Detrimental Effects of E. coli Proliferation

The nucleotide sequences for the exogenous identified sequences were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia, CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 1) and 5' - ACAATTTCACACAGCCTC - 3' (SEQ ID NO: 2). These sequences flank the polylinker in pLEX5BA. Sequence identification numbers (SEQ ID NOs) for the identified inserts are listed in Table I and discussed below.

#### **EXAMPLE 3**

#### Comparison Of Isolated Sequences to Known Sequences

The nucleic acid sequences of the subcloned fragments obtained from the expression vectors discussed above were compared to known *E. coli* sequences in GenBank using BLAST version 1.4 or version 2.0.6 using the following default parameters: Filtering off, cost to open a gap=5, cost to extend a gap=2, penalty for a mismatch in the blast portion of run=3, reward for a match in the blast portion of run=1, expectation value (e)=10.0, word size=11, number of one-line descriptions=100, number of alignments to show (B)=100. BLAST is described in Altschul, J Mol Biol. 215:403-10 (1990). Expression vectors were found to contain nucleic acid sequences in both the sense and antisense orientations. The presence of known genes, open reading frames, and ribosome binding sites was determined by comparison to public databases holding genetic information and various computer programs such as the Genetics Computer Group programs FRAMES and CODONPREFERENCE. Clones were designated as "antisense" if the cloned fragment was oriented to the promoter such that the RNA transcript produced was complementary to the expressed mRNA from a chromosomal locus. Clones were designated as "sense" if they coded for an RNA fragment that was identical to a portion of a wild type mRNA from a chromosomal locus.

The sequences described in Examples 1-2 that inhibited bacterial proliferation and contained gene fragments in an antisense orientation are listed in Table I. This table lists each identified sequence by: a sequence identification number; a Molecule Number; a gene to which the identified sequence corresponds, listed according to the National Center for Biotechnology Information (NCBI), Blattner

(Science 277:1453-1474(1997); also contains the *E. coli* K-12 genome sequence), or Rudd (Micro. and Mol. Rev. 62:985-1019 (1998)), nomenclatures. The CONTIG numbers for each identified sequence is shown, as well as the location of the first and last base pairs located on the *E. coli* chromosome. A Molecule Number with a "\*\*" indicates a clone corresponding to an intergenic sequence.

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TABLE I

Identified Clones with Corresponding Genes and Operons

Clone Name	Seq	Molecule	Gene	Gene	Gene ·	Contig	Start	Stop
	<b>ID</b> .	No.	(NCBI)	(Blat-	(Rudd)	•		
				tner)	•			
626.O24	1	EcXA056	f320	b1113	ycfS	AE000211	7631	7971
E1M10000116B1	2	EcXA056b	ycfS	b1113	ycfS	AE000211	7658	7847
E1M10000155F12	3	EcXA056c	ycfS	b1113	ycfS	AE000211	7649	8037
Z56-D2	4	EcXA057	arp	b4017	arp	AE000474	14059	14440
E1M10000144B6	5	EcXA057b	arp	ь4017	агр	AE000474	14187	14385
Z60-P16	6	EcXA058	rplC	ь3320	rplC	AE000408	10002	10338
Z80-D10	7	EcXA059	урјА	b2647	ypjA	AE000349	10402	10493
						AE000350	1	728
P33-1.C22	8	EcXA060	rplR	b3304	rplR	AE000408	2763	2958
E1M10000161C06	9	EcXA060b	RplR;	b3304;	RplR;	AE000408	3006	3477
			rplF	b3305	rplF			
P35-7	10	EcXA061	malE	b4034	malE	AE000476	11925	12089
P35-8	11	EcXA062	rep	ь3778	rep	AE000454	4438	4111
P38-1.G20	12	EcXA063	elaD	b2269	elaD	AE000316	9912	9581
E1M10000107H4	13	EcXA063b	elaD	b2269	elaD	AE000316	9520	9389
E1M10000122B03	14	EcXA063c	elaD	b2269	elaD	AE000316	9979	9715
E1M10000139B07	15	EcXA063d	elaD	b2269	claD	AE000316	10171	9533
E1M10000152G3	16	EcXA063e	elaD	b2269	elaD	AE000316	9535	9406
E1M10000143G03	17	EcXA063f	elaD	b2269	claD	AE000316	10104	9869
E1M10000131H01	18	EcXA063h	elaD	b2269	elaD	AE000316	9953	9746
P319-4.06	19	EcXA064	CyoE	b0428	суоЕ	AE000149	2140	2293
P323-1.M10	20	EcXA065	DgoA	b3692	YidU	AE000446	6005	6272
E1M10000111E4	21	EcXA065b	DgoA	b3692	YidU	AE000446	6005	6133
P323-8.P1	22	EcXA066	Rpml	b1717	RpmI	AE000266	10240	10390

Clone Name	Seq	Molecule	e Gene Gene Gene		Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000137G09	23	EcXA066b	RplT;r	b1716;	RplT;	AE000266	9947	10525
			pmI	b1717	RpmI			
P326-22.E17	24	EcXA067	xylF	b3566	XylF	AE000434	288	95
P326-9.K2	25	EcXA068	YhfL;	b3369;	yhfL;	AE000413	581	306
			yhfM	ь3370	yhfM			
P327-50.M10	26	EcXA069	RplD;	b3319;	rplD;	AE000408	9747	9900
			rplC	b3320	rplC			
E1M10000110G1	27	EcXA069b	RplD;	b3319;	rplD;	AE000408	9789	9933
			rplC	ь3320	rplC			
E1M10000121D08	28	EcXA069c	RplD;	b3319;	RpID;	AE000408	9737	10002
			rplC	ь3320	rplC			
Е1М10000136Н1	29	EcXA069d	RplD;	b3319;	RplD;	AE000408	9707	10241
			rplC	ь3320	rplC			
E1M10000126E08	30	EcXA069c	rplC	ь3320	RpIC	AE000408	10157	10379
E1M10000137C04	31	EcXA069f	RplD;	b3319;	RplD;	AE000408	9783	10007
ţ			rplC	b3320	RplC '			
E1M10000106G02	32	EcXA069g	rplC	b3320	RpIC	AE000408	9814	10154
E1M10000146H01	33	EcXA069h	RplD;	ь3319;	RpID;	AE000408	9715	9890
			rplC	ь3320	RplC			
E1M10000148C02	34	EcXA069i	RplD;	ьзз19;	RpID;	AE000408	9740	9980
			rplC	ь3320	RpIC			
P328-20.P20	35	EcXA070	YbcQ	b0551	YbcQ	AE000160	7883	7661
1065-12	36	EcXA071	ffh	b2610	Ffh	AE000346	11978	12129
						AE000347	1	319
E1M10000101D6	37	EcXA071b	RpsP;	b2609;	RpsP;	AE000346	11911	12129
			ffh	ь2610	ffh			
						AE000347	1	348
P332-11.C20	38	EcXA072	recJ	ь2892	recJ	AE000372	12047	12144
						AE000273	1	108
P334-5.H2	39	EcXA073	htrE	ь0139	htrE	AE000123	5431	5548
P338-4.M21	40	EcXA073b	htrE	b0139	htrE	AE000123	5447	5593
E1M10000119A04	41	EcXA073c	htrE	ь0139	htrE	AE000123	5419	5642
E1M10000137C03	42	EcXA073d	htrE;	ь0139;	htrE;	AE000123	5414	5919
			ecpD	ь0140	ecpD			
E1M10000124G03	43	EcXA073c	htrE	ь0139	htrE	AE000123	5332	5515
P334-8.L7	44	EcXA074	yciR	b1285	yciŘ	AE000226	8045	8371
1053-37	45	EcXA074b	yciR	ь1285	yciR	AE000226	6079	6293
P335-3.J14	46	EcXA075	SfmD	b0532	sfmD	AE000159	3235	3115
P335-8.H8	47	EcXA076	mviM	ь1068	mviM	AE000207	11140	10983
						AE000208	50	1
P342-3	48	EcXA077	B2145	b2145	yeiS	AE000303	9025	8831

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	LD	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000106G10	49	EcXA077b	B2145	b2145	yeiS	AE000303	9007	8841
E1M10000144F3	50	EcXA077c	B2145	b2145	yeiS	AE000303	9052	8827
X3S177-4	51	EcXA078	ycgB	Ы 188	ycgB	AE000217	3945	4129
P317-2.A3	52	EcXA079	yedV	Ы968	yedX	AE000288	5289	5475
E1M10000151C04	53	EcXA079b	yedV	b1968	yedV	AE000288	5179	5515
E1M10000162G05	54	EcXA079c	yedV	ь1968	yedV	AE000288	5313	5503
E1M10000167F04	55	EcXA079d	yedV	ь1968	yedV	AE000288	5293	5531
E1M10000167G04	56	EcXA079e	yedV	ь1968	y <b>ed</b> V	AE000288	5293	5531
X3S204-7	57	EcXA080	rplV	b3315	RplV	AE000408	7444	7770
E1M10000111C3	58	EcXA080b	RplV;	b3315;	RplV;	AE000408	7633	7898
			rpsS	b3316	rpsS			
E1M10000131B07	59	EcXA080c	RpIV;	b3315;	RpIV;	AE000408	7686	7871
			rpsS	b3316	rpsS			
E1M10000131C07	60	EcXA080d	RplV;	b3315;	RplV;	AE000408	7723	7860
·			rpsS	b3316	rpsS ·			
E1M10000144G6	61	EcXA080e	rplV	b3315	RpIV	AE000408	7580	7762
E1M10000144C2	62	EcXA080f	RplV;	b3315;	RpIV;	AE000408	7650	7784
			rpsS	b3316	rpsS			
E1M10000107G2	63	EcXA081	rpsP	b2609	RpsP	AE000346	11957	12097
MC9.6	64	EcXA082	hybC;	b2994;	HybC;	AE000382	4419	4562
			hybB	b2995	hybB			
B18-2.N21	65	EcXA083	hrpB	b0148	HrpB	AE000124	3024	2955
P336-14.F20	66	EcXA084	B1399	b1399	PaaX	AE000237	164	1
						AE000236	12073	12006
985.P21	67	EcXA085	AgaZ;	b3132;	agaZ;	AE000394	10111	10705
			agaV	b3133	agaV			
Z92-K24	68	EcXA086	rplQ	b3294	RplQ	AE000407	7653	8349
E1M10000101C12	69	EcXA086b	rplQ	b3294	RplQ	AE000407	7748	8075
E1M10000103D11	70	EcXA086c	RplQ	b3294	RplQ	AE000407	7652	8051
E1M10000127D09	71	EcXA086d	rplQ;	ь3294;	RpIQ;	AE000407	7806	8129
			rpo∧	b3295	rpoA			
E1M10000152D8	72	EcXA086e	rplQ;	b3294;	rplQ;	AE000407	7950	8146
			rpoA	b3295	rpoA			
SC17.1	73	EcXA087	YehW	b2128	YehW	AE000302	915	1226
SC21.1	74	EcXA088	RplO	b330l	RplO	AE000408	1743	1907
E1M10000107G8	75	EcXA089	YadT	ь0158	YadT	AE000125	4489	4639
E1M10000115C6	76	EcXA090	DnaE	ь0184	DnaE	AE000127	10980	10830
E1M10000107B2	77	EcXA091	YkgE	b0306	YkgE	AE000137	9375	9261
E1M10000107C3	78	EcXA092	ь1497	ь1497	YdcM	AE000247	689	908
E1M10000107H9	79	EcXA093	YohM	b2106	YohM	AE000299	9423	9166
E1M10000109A11	80	EcXA094	YfjW	b2642	YfjW	AE000349	7160	6851

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000160D07	81	EcXA094b	YfjW	b2642	YfjW	AE000349	7118	6932
E1M10000161A05	82	EcXA094c	YfjW	b2642	YfjW	AE000349	6381	5980
E1M10000155A06	83	EcXA094d	YfjW	b2642	YfjW	AE000349	6893	6749
E1M10000111A7	84	EcXA095	ь2758	b2758	YgcJ	AE000359	4983	5069
E1M10000107E2	85	EcXA096	YgcM;	b2765;	ygcM;	AE000360	5320	5190
			ygcN	b2766	ygcN			
E1M10000115E3	86	EcXA097	yhcB	b3233	YhcB	AE000402	8070	7864
EIM10000107B3	87	EcXA097b	yhcB;	b3233;	yhcB;	AE000402	8168	7922
			degQ	b3234	degQ			
E1M10000162F03	88	EcXA097c	yhcB	b3233	yhcB	AE000402	8111	7874
E1M10000127H07	89	EcXA097d?	yhcB	b3233	yhcB	AE000402	8092	7808
E1M10000163C04	90	EcXA097e	yhcB;	b3233;	yhcB;	AE000402	8159	7874
			degQ?	b3234	degQ			
E1M10000115G2	91	EcXA098	rpoA	b3295	RpoA	AE000407	8254	8453
E1M10000144A8	92	EcXA098b	RplQ;	b3294;	RpIQ;	AE000407	7841	8118
			rpoA	b3295	rpoA			
E1M10000101H9	93	EcXA099	RpsN;	b3307;	RpsN;	AE000408	4403	4826
			rplE	b3308	RplE			
EIM10000111F9	94	EcXA100	RpmH;	ь3703;	RpmH;	AE000447	7555	7395
			mpA	b3704	RnpA			
E1M10000119D02	95	EcXA100b	rpmH;	b3703;	RpmH;	AE000447	7581	7395
			mpA	b3704	RnpA			
E1M10000106F05	96	EcXA100c	rpmH;	b3703;	RpmH;	AE000447	7594	7359
			mpA	ь3704	RnpA			
E1M10000152H8	97	EcXA100d	RpmH;	b3703;	RpmH;	AE000447	7630	7340
		•	mpA	ь3704	RnpA			
E1M10000115H1	98	EcXA101	yihK	b3871	ТурА	AE000462	8811	8629
E1M10000101H7	99	EcXA102	adiY	b4116	AdiY	AE000484	1980	2171
E1M10000109A02	100	EcXA103	yjhB	b4279	YjhB	AE000498	8776	8536
E1M10000113A11	101	EcXA104	hsdS	b4348	HsdS	AE000505	6319	6495
E1M10000125A2	102	EcXA104b	hsdS	b4348	HsdS	AE000505	6277	6526
E1M10000103A5	103	EcXA105	ydaU	b1359	YdaU	AE000233	4497	4306
E1M10000135B2	104	EcXA106	ybbV	ь0510	YbbV	AE000157	3796	3624
E1M10000131G10	105	EcXA106	ybbV	ь0510	YbbV	AE000157	3796	3624
E1M10000110A12	106	EcXA107	yegO	ь2076	YegO	AE000297	14471	14330
E1M10000110E9	107	EcXA108	yigK	ь3824	YigK	AE000458	3709	3964
E1M10000133A06	108	EcXA109	modC	ь0765	ModC	AE000179	2414	2180
E1M10000133B08	109	EcXA110	ynaF;	b1376;	YnaF;	AE000234	8011	8149
			ь1377	ь1377	OmpN			
E1M10000106E09	110	EcXA110b	ynaF;	b1376;	YnaF;	AE000234	7967	8207
			ь1377	ь1377	OmpN			

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000160G07	111	EcXA110c	ynaF;	b1376;	YnaF;	AE000234	7990	8114
			b1377	b1377	OmpN			
SC13.1	112	EcXA110d	ynaF	b1376	YnaF	AE000234	8027	8243
E1M10000155B05	113	EcXA110e	ynaF;	b1376;	YnaF;	AE000234	7992	8139
			b1377	ь1377	ompN			
E1M10000133D09	114	EcXA111	ppdA	b2826	PpdA	AE000366	4876	5068
E1M10000162B08	115	EcXA111b	ppdA	b2826	PpdA	AE000366	4968	5084
E1M10000133E01	116	EcXA112	yrfF	b3398	YrfF	AE000415	5835	5712
E1M10000101A7	117	EcXA113	ybbQ;	ь0509;	YbbQ;	AE000157	3753	3466
			ybbV	ь0510	ybbV			
E1M10000131F04	118	EcXA113b	ybbQ;	ь0509;	YbbQ;	AE000157	3781	3536
			ybbV	ь0510	ybbV			
E1M10000159A09	119	EcXA113c	ybbQ;	ь0509;	YbbQ;	AE000157	3781	3257
			ybbV	ь0510	ybbV			
E1M10000166F09	120	EcXA113d	ybbV	ь0510	YbbV	AE000157	3784	3624
E1M10000121E07	121	EcXA114	b2352;	b2352;	YfdH;	AE000323	10110	9882
			b2353	b2353	yfdl			
						AE000324	357	1
E1M10000121F06	122	EcXA115	ygeF	b2850	YgeF	AE000369	570	304
E1M10000140B05	123	EcXA115b	ygcF	ь2850	YgeF	AE000369	512	312
E1M10000148H09	124	EcXA115c	ygeF	b2850	YgeF	AE000369	607	361
E1M10000164A02	125	EcXA115d	ygcF	b2850	YgcF	AE000369	555	411
E1M10000121G05	126	EcXA116	insB_3	ь0021		AE000135	5258	5726
E1M10000136D3	127	EcXA117	rhsA	b3593	RhsA	AE000437	4125	3529

**EXAMPLE 4** 

#### Identification of Genes and their Corresponding Operons Affected by Antisense Inhibition

The sequencing of the entire E. coli genome is described in Blattner et al., Science 277:1453-5 . 1474(1997) and the sequence of the genome is listed in GenBank Accession No.U00096. The operons to which the proliferation-inhibiting nucleic acids correspond were identified using RegulonDB and information in the literature. The coordinates of the boundaries of these operons on the E. coli genome are listed in Table III. Table II lists the molecule numbers of the inserts containing the growth inhibiting nucleic acid fragments, the genes in the operons corresponding to the inserts, the SEQ ID NOs of the genes containing the inserts, the SEQ ID NOs of the proteins encoded by the genes, the start and stop points of the genes on the E. coli genome, the orientation of the genes on the genome, whether the operons are predicted or documented, and the predicted functions of the genes. The identified operons, their putative functions, and whether or not the genes are presently thought to be required for proliferation are discussed below.

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Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. The functions for the genes of interest appear in Table II.

The proteins that are listed in Table II are involved in a wide range of biological functions.

TABLE II

All Operon Data with Whole Chromosome Coordinates

Molecule Number	Gene	Seq ID No.	Seq ID No.	Start	Stop	Operon	Blattner Functional Class	Predicted Function
		(gene)	(protein)					
EcXA056	ycfS	128	299	1168635	1169597	predicted operon	hypothetical, unclassified, unknown	
EcXA057	arp	129	300	4217880	4220066	predicted operon	Fatty acid and phospholipid metabolism	ankyrin repeat protein
EcXA058	rpsQ	130	301	3445951	3446205	documented	Translation, post- translational modification	
	rpmC	131	302	3446205	3446396		Translation, post- translational modification	
	rplP	132	303	3446396	3446806		Translation, post- translational modification	
	rpsC	133	304	3446819	3447520		Translation, post- translational modification	
	rplV	134	305	3447538	3447870		Translation, post- translational modification	
	rpsS	135	306	3447885	3448163		Translation, post- translational modification	
	rplB	136	307	3448180	3449001		Translation, post- translational modification	translation
	rplW	137	308	3449019	3449321		Translation, post- translational modification	translation
	rplD	138	309	3449318	3449923		Translation, post- translational modification	l,
	rplC	139	310	3449934	3450563		Translation, post- translational modification	
	rpsJ	140	311	3450596	3450907		Translation, post- translational modification	
EcXA059	урјА	141	·312	2776167	2780876	predicted operon	Translation, post- translational modification	
EcXA060	rpmJ	142	313	3440255	3440371	documented	Translation, post- translational modification	
	prlA	143	314	3440403	3441734		Putative transport proteins	
	rp!O	144	315	3441742			Translation, post- translational modification	
	rpmD	145	316	3442180	3442359		Translation, post- translational modification	
	rpsE	146	317	3442363	3442866		Translation, post- translational modification	į

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Molecule Number	Gene	Seq ID No.	Seq ID No.	Start	Stop	Operon	Blattner Functional Class	Predicted Function
		(gene)	(protein)					
	rplR	147	318	3442881	3443234		Translation, post- translational modification	
	rplF	148	319	3443244	3443777		Translation, post- translational modification	translation
	rpsH	149	320	3443790	3444182		Translation, post- translational modification	·
	rpsN	150	321	3444216	3444521		Translation, post- translational modification	
	rplE	151	322	3444536	3445075		Translation, post- translational modification	translation
	rplX	152	323	3445090	3445404		Translation, post- translational modification	
	rplN	153	324 .	3445415	3445786		Translation, post- translational modification	
EcXA061	malE	154	325	4242808	4243998	documented	Transport and binding proteins	
•	malF malG	155 156	326 327	4241110	4242654 4241095		Transport and binding proteins Transport and binding	
	maig	130	327	4240203	4241093		proteins	: ;
EcXA062	гер	157	328	3958292	3960313	predicted operon	DNA replication, recombination,	
D 37.4662	10060		200	2222	2201044	* . *	modification and repair	
EcXA063	b2269	158	329	2380733	2381944	predicted operon	Putative enzymes	putative phosphatase/sulfatase
EcXA064	cyoE	159	330	446039	446929	documented	Energy metabolism	
	cyoA	160	331	449887	450834		Energy metabolism	
	cyoB	161	332	447874	449865		Energy metabolism	
	суоС	162	333	447270	447884		Energy metabolism	
	cyoD	163	334	446941	447270		Energy metabolism	
EcXA065	dgoA	164	335	3869477	3871240	predicted	Carbon compound catabolism	2-Oxo-3- deoxygalactonate 6- phosphate aldolase
	dgoK	165	336	3871224	3872401		Carbon compound	
	yidW	166	337	3872401	3872787		Hypothetical, unclassified, unknown	
	b3694	167	338		3872395		Putative regulatory protein	
EcXA066	rpIT	168	339		1797773	documented	Translation, post- translational modification	
	rpmI	169	340	1797826			Translation, post- translational modification	
	infC	170	341		1798662		Translation, post- translational modification	translation
	thrS	171	342	1798666	1800594		Translation, post- translational modification	
EcXA067	xylF	172	343	3728760	3729752	:	Transport and binding proteins	
EcXA068	yhfL	173	344	3497085	3497252	predicted operon	Hypothetical, unclassified, unknown	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number		No.	No.		•	•	Class	
		(gene)	(protein)					
	yhfM	174	345	3497496	3498884	predicted operon	Putative Transport	;
	yhfN	175	346	3498884	3499927		Putative Transport	:
	yhfO	176	347	3499890	3500339		Hypothetical, unclassified, unknown	
EcXA069		x	x			same operon as EcXA058		
EcXA070	ybcQ	177	348	573179	573562	predicted operon	Hypothetical, unclassified, unknown	
EcXA071	fth	178	349	2744454	2745815	predicted operon	Transport and binding proteins	
EcXA072	recJ	179	350	3034393	3036126	predicted operon	Transcription, RNA processing and degradation	
	dsbC	180	351	3036132	3036842		Cell structure	
	xerD	181	352	3036867	3037763		DNA replication, recombination, modification and repair	
EcXA073	ecpD	182	353	155461	156201	documented	Cell structure	
	htrE	183	354	152829	155426		Cell structure	
EcXA074	yciR	184	355	1342781	1344766	predicted operon	Hypothetical, unclassified, unknown	
EcXA075	sfmC	185	356	558197	558889	predicted operon	Putative chaperonin	
	sfmD	186	357	558920	561523		Cell structure	
	sfmH	187	358	561565	562542		Cell processes (incl. adaptation, protection)	
	sfmF	188	359	562553	563068		Cell processes (incl. adaptation, protection)	
EcXA076	Lmin	189	360	1124785	1125369	predicted operon	Translation, post- translational modification	
	yceH	190	361	1125380	1126027		Hypothetical, unclassified, unknown	
	mviM	191	362	1126029	1126952		Cell processes (incl. adaptation, protection)	
EcXA077	sanA	192	363	2230898	2231617	predicted		
	b2145	193	364	2231620	2231859		Hypothetical,	
EcXA078	ycgB	194	365	1234932	1236464	predicted operon	unclassified, unknown Hypothetical, unclassified, unknown	
EcXA079	yedV	195	366	2034816	2036174	predicted	Hypothetical, unclassified, unknown	
	yedW	196	367	2036174	2036893		Hypothetical, unclassified, unknown	
EcXA080		x	x			same operon as EcXA058		
EcXA081	b2107	197	368	2184800	2185318	predicted	Hypothetical, unclassified, unknown	
	ь2106	198	369	2183937	2184761		Hypothetical, unclassified, unknown	
EcXA082	hybG	199	370	3137731	3137979	documented	Energy metabolism	
	hybF	200	371	3137992			Energy metabolism	
L	hybE	201	372	3138326	3138814		Energy metabolism	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number		No.	No.				Class	
		(gene)	(protein)					
	hybD	202	373	3138807	3139301		Energy metabolism	
	hybC	203	374	3139301	3141004		Energy metabolism	
1	hybB	204	375	3141001	3142179		Energy metabolism	
F-VA002	hybA	205	376	3142169 162060	3143155 164534		Energy metabolism Transcription, RNA	
EcXA083	hrpB	206	377	102000	104334		processing and	
							degradation	
FcXA084	ь1399	207	378	1461563	1462513		Hypothetical,	
	•						unclassified, unknown	
	b1400	208	379	1462495	1463085		Hypothetical,	
							unclassified, unknown	
EcXA085	agaZ	209	380	3276555	3277835	predicted	Carbon compound catabolism	putative tagatose 6- phosphate kinase 2
	agaV	210	381	3277822	3278331		Central intermediary metabolism	PTS system, (EIIB-AGA)
	agaW	211	382	3278342	3278743		Central intermediary metabolism	PTS system (EIIC)
-	agaA	212	383	3278763	3279266		Central intermediary metabolism	putative N-NAG-6- phosphatedeacetylase
	agaS	213	384	3279617	3280771		Central intermediary metabolism	putative tagatose-6- phosphate aldose/ketose isomerase
	agaY	214	385	3280784	3281644		Central intermediary metabolism	tagatose-bisphosphate aldolase 2
EcXA086	rpsM	215	386	3439752	3440108	documented	Translation, post- translational modification	
	rpsK	216	387	3439346	3439735		Translation, post- translational modification	
	rpsD	217	388	3438692	3439312		Translation, post- translational modification	
	гроА	218	389	3437677	3438666		Translation, post- translational modification	
	rplQ	219	390	3437253	3437636		Translation, post- translational modification	•
EcXA087	ychW	220	391	2213765	2214496	predicted	Hypothetical, unclassified, unknown	
	yehX	221	392		2215427		Hypothetical, unclassified, unknown	·
	yehY	222	393		2216577 2217501		Hypothetical, unclassified, unknown Hypothetical,	:
EcXA088	yehZ	223 x	394 x	2216584	2217301	same as	unclassified, unknown	
						EcXAO60		
EcXA089	yadS	224	395	177662	178462	predicted operon	Hypothetical, unclassified, unknown	
	yadT	225	396	177662	178462		Hypothetical, unclassified, unknown	
,	pſs	226	397	178455	179153		andustrieu, mianuwii	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number		No. (gene)	No. (protein)				Class	
EcXA090	lpxA	227	398	202560	203348	predicted		
						operon		
	lpxB	228	399	203348	204496			
	mhB dnaE	229 230	400 401	204493 205126	205089			RnaaseH 2
	unae	230	401	203120	208608			DNA pol III subunit
EcXA091	ykgE	231	402	320832	321551	predicted	Hypothetical, unclassified, unknown	
	ykgF	232	403	321562	322989		Hypothetical, unclassified, unknown	
	ykgG	233	404	322829	323677		Hypothetical, unclassified, unknown	
EcXA092	b1497	234	405	1577657	1578829	predicted	Hypothetical, unclassified, unknown	
	b1498	235	406	1578866	1580581		Hypothetical, unclassified, unknown	
EcXA093	yohM	236	407	2183937	2184761	predicted	Hypothetical,	
	b2107	237	408	2184800	2185318		unclassified, unknown Hypothetical,	
EcXA094	yfjW	238	409	2771339	2773042	predicted	unclassified, unknown Hypothetical,	
EcXA095	b2758	239	410	2879074	2880165	predicted	unclassified, unknown Hypothetical,	
EcXA096	удсМ	240	411	2890237	2890602	predicted	unclassified, unknown Hypothetical, unclassified, unknown	
	ygcN	241	412	2890650	2891951		Hypothetical, unclassified, unknown	
	b2767	242	413	2891906	2892202		Hypothetical, unclassified, unknown	
	b2768	243	414	2892219	2892794		Hypothetical, unclassified, unknown	
EcXA097	yhcB	244	415	3377820	3378224	predicted operon	Hypothetical, unclassified, unknown	
	hhoA (degQ)	245	416	3378378	3379745	predicted operon	Translation, post- translational modification	
	hhoB	246	417	3379835	3380902		Translation, post- translational modification	
EcXA098	rpsM	247	418	3439752	3440108	documented	Translation, post- translational modification	
	rpsK	248	419	3439346	3439735		Translation, post- translational modification	
	rpsD	249	420	3438692	3439312		Translation, post- translational modification	
	гроА	250	421	3437677	3438666		Translation, post- translational modification	
	rplQ	251	422	3437253	3437636		Translation, post- translational modification	
EcXA099		x	x			same as EcXA060		
EcXA100	rpmH	252	423	3881965	3882105	documented	Translation, post- translational modification	
	mpA	253	424	3882122	3882481		DNA replication, recombination, modification and repair	

Molecule Number	Gene	Seq ID No. (gene)	Seq ID No. (protein)	Start	Stop	Operon	Blattner Functional Class	Predicted Function
EcXA101	yihK	254	425	4055987	4057762	predicted operon	Hypothetical, unclassified, unknown	
EcXA102	adi	255	426	4335832	4338102	documented	Putative regulatory proteins	biodegradative acid- induced arginine decarboxylase
	adiY	256	427	4334746	4335507		Amino acid biosynthesis and metabolism	
EcXA103	yjhB	257	428	4501566	4502843	predicted operon	Hypothetical, unclassified, unknown	
	yjhC	258	429	4502840	4503973		Hypothetical, unclassified, unknown	
EcXA104	hsdS	259	430	4577638	4579032	documented	DNA replication, recombination, modification and repair	host specificity
	hsdM	260	431	4579029	4580618		DNA replication, recombination, modification and repair	
EcXA105	ь1357	261	432	1418389	1418685	predicted	Hypothetical, unclassified, unknown	
	b1358	262	433	1418708	1419130		Hypothetical, unclassified, unknown	
	ydaU	263	434	1419143	1420000		Hypothetical, unclassified, unknown	!
	b1360	264 265	435 436	1420007 1420725	1420753 1421336		Hypothetical, unclassified, unknown Hypothetical,	:
	b1361 b1362	266	436	1420723	1421556		unclassified, unknown  Hypothetical,	
EcXA106	ybbQ	267	438	535810	536688	predicted	unclassified, unknown Hypothetical,	
	ybbV	268	439	536720	536998		unclassified, unknown Hypothetical,	
	ь0511	269	440	536998	538311		unclassified, unknown Hypothetical, unclassified, unknown	
EcXA107	yegM	270	441	2151891	2153285	predicted	Hypothetical, unclassified, unknown	
	yegN	271	442	2153285	2156407		Hypothetical, unclassified, unknown	
	yegO	272	443		2159485		Hypothetical, unclassified, unknown	
EcXA108	yegB yigK	273 274	444 445		2160901 4006462		Hypothetical, unclassified, unknown Hypothetical,	
EcXA109	modA	275	446	794312	795085	documented	unclassified, unknown Transport and binding	molybdate uptake
	modB	276	447	795085	795774		proteins Transport and binding	
	modC	277	448	795777	796835		proteins Transport and binding	
EcXA110	ynaF	278	449	1433209	1433715	predicted	proteins Hypothetical, unclassified, unknown	
	b1377	279	450	1433784	1434917	predicted	Hypothetical, unclassified, unknown	
EcXA111	гесС	280	451	2957082	2960450	predicted	Transcription, RNA processing and	

Molecule Number	Gene	Seq ID No. (gene)	Seq ID No. (protein)	Start	Stop	Operon	Blattner Functional Class	Predicted Function
		(Gene)	(protat)				degradation	
	ppdC	281	452	2960463	2960786		Other known genes	prepilin peptidase dependent protein C
	ygdB	282	453	2960771	2961136		Hypothetical, unclassified, unknown	
	ppdB	283	454	2961175	2961738		Other known genes	prepilin peptidase dependent protein B
	ppdA	284	455	2961729	2962199		Other known genes	prepilin peptidase dependent protein A
EcXA112	yrff	285	456	3524107	3526242	predicted	Hypothetical, unclassified, unknown	
	yrfG	286	457	3526262	3526975		Hypothetical, unclassified, unknown	
	упН	287	458	3526986	3527387		Hypothetical, unclassified, unknown	
	yrfl	288	459	3527406	3528290		Hypothetical, unclassified, unknown	
EcXA113		x	x			same as EcXA106		
EcXA114	b2350	289	460	2465875	2466237	predicted	Hypothetical, unclassified, unknown	
	b2351	290	46 I	2466234	2467154		Hypothetical,	
	b2352	291	462	2467151	2468482		unclassified, unknown Hypothetical,	
	b2353	292	463	2468781	2469125	predicted	unclassified, unknown Hypothetical,	
EcXA115	ygeF	293	464	2988576	2989022	predicted	unclassified, unknown Hypothetical,	
EcXA116	insB_3	294	465	289873	290376	predicted	unclassified, unknown phage, transposon, or	
	insA_3	295	466	290295	290570		plasmid phage, transposon, or	
EcXA117	rhsA	296	467	3759810	3763943	predicted	plasmid Hypothetical,	
	yibA	297	468	3763964	3763806		unclassified, unknown Hypothetical,	
	yibJ	298	469	3764848	3765549		unclassified, unknown Hypothetical, unclassified, unknown	

Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. Biological functions for genes that lie on the same operon as an identified gene have also been made. The functions for the genes of interest appear in Table II.

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The genes of interest have a variety of biological functions. For example, genes that are thought to function as transport or binding proteins, that participate in translation or post-translational modification, that are involved in carbon compound catabolism, that are thought to be enzymes,

participate in cell processes, energy metabolism and biosynthetic functions appear in Table II. Genes that are involved in cell structure, transcription, RNA processing and degradation also appear in Table II.

Several of the expression vectors contain fragments that correspond to genes of unknown function or if the function is known, it is not known whether the gene is essential. For example, EcXA056, 057, 059, 063, 064, 065, 067, 068, 070, 073, 074, 075, 076, 077, 078, 079, 081, 084, 085, 087, 089, 091, 092, 093, 094, 095, 096, 097, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 and 117 are all exogenous nucleic acid sequences that correspond to *E. coli* proteins that have no known function or where the function has not been shown to be essential or nonessential.

The present invention reports a number of novel *E. coli* genes and operons that are required for proliferation. From the list of clone sequences identified here, each was identified to be a portion of a gene in an operon required for the proliferation of *E. coli*. Cloned sequences corresponding to genes already known to be required for proliferation in *E. coli* include EcXA058, 060, 066, 069, 071, 080, 086, 088, 090, 098, 099 and 100 are exogenous nucleic acid sequences that correspond to *E. coli* genes that are known to be required for cellular proliferation. The remaining identified sequences correspond to *E. coli* genes previously undesignated as required for proliferation in the art.

An interesting observation of the present invention is that there are also several sequence fragments that correspond to *E. coli* genes that are not thought to be required for *E. coli* proliferation. Nevertheless, under the conditions described above, the antisense expression of these gene fragments causes a reduction in cell growth. This result implies that the genes corresponding to the identified sequences are actually required for proliferation or are in operons required for proliferation. Molecule Nos. corresponding to these genes are EcXA061, 062, 072, 082, 083, 104 and 116.

Following identification of the sequences of interest, these sequences were localized into operons. Since bacterial genes are expressed in a polycistronic manner, the antisense inhibition of a single gene in an operon might effect the expression of all the other genes on the operon or the genes down stream from the single gene identified. In order to determine which of the gene products in an operon are required for proliferation, each of the genes contained within an operon may be analyzed for their effect on viability as described below.

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TABLE III
Operon Boundaries

Molecule	Start	Stop
Number		
EcXA056	1168635	1169597
EcXA057	4217880	4220066
EcXA059	2776167	2780876
EcXA061	4240205	4243998
EcXA062	3958292	3960313
EcXA063	2380733	2381944
EcXA064	446039	450834
EcXA065	3869477	3872395
EcXA067	3728760	3729752
EcXA068	3497085	3500339
EcXA070	573179	573562
EcXA071	2744454	2745815
EcXA072	3034393	3037763
EcXA073	152829	156201
EcXA074	1342781	1344766
EcXA075	558197	563068
EcXA076	1124785	1126952
EcXA077	2230898	2231859
EcXA078	1234932	1236464
EcXA079	2034816	2036893
EcXA081	2183937	2185318
EcXA082	3137731	3143155
EcXA083	162060	164534
EcXA084	1461563	1463085
EcXA085	3276555	3280771
EcXA086	3437253	3440108
EcXA087	2213765	2217501
EcXA089	177662	179153
EcXA090	202560	208608
EcXA091	320832	323677
EcXA092	1577657	1580581
EcXA093	2183937	2185318
EcXA094	2771339	2773042
EcXA095	2879074	2880165
EcXA096	2890237	2892794

Molecule	Start	Stop
Number		
EcXA097	3377820	3380902
EcXA098	3437253	3438666
EcXA100	3881965	3882481
EcXA101	4055987	4057762
EcXA102	4334746	4338102
EcXA103	4501566	4503973
EcXA104	4577638	4580618
EcXA105	1418389	1421668
EcXA106	535810	538311
EcXA107	2151891	2160901
EcXA108	4006046	4006462
· EcXA109	794312	796835
EcXA110	1433209	1434917
EcXA111	2957082	2962199
EcXA112	3524107	3528290
EcXA114	2465875	2469125
EcXA115	2988576	2989022
EcXA116	289873	290570
EcXA117	3759810	3765549

# **EXAMPLE 5**Identification of Individual Genes within an Operon Required for Proliferation

The following example illustrates a method for determining which gene in an operon is required for proliferation. The clone insert corresponding to Molecule No. EcXA066 possesses nucleic acid sequence homology to the *E. coli* genes *rplT* and *rpml*. These genes are located in an operon containing two additional genes, *infC* and *thrS*. To determine which gene or genes in this operon are required for proliferation, each gene is selectively inactivated using homologous recombination. Gene *rplT* is the first gene to be inactivated.

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Deletion inactivation of a chromosomal copy of a gene in *E. coli* can be accomplished by integrative gene replacement. The principle of this method (Hamilton, C. M., et al 1989. *J. Bacteriol.* 171: 4617-4622) is to construct a mutant allele of the targeted gene, introduce that allele into the chromosome using a conditional suicide vector, and then force the removal of the native wild type allele and vector sequences. This will replace the native gene with a desired mutation(s) but leave promoters, operators, etc. intact. Essentiality of a gene is determined either by deduction from genetic analysis or by conditional expression of a wild type copy of the targeted gene (trans complementation).

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The first step is to generate a mutant rplT allele using PCR amplification. Two sets of PCR primers are chosen to produce a copy of rplT with a large central deletion to inactivate the gene. In order to eliminate polar effects, it is desirable to construct a mutant allele comprising an in-frame deletion of most or all of the coding region of the rplT gene. Each set of PCR primers is chosen such that a region flanking the gene to be amplified is sufficiently long to allow recombination (typically at least 500 nucleotides on each side of the deletion). The targeted deletion or mutation will be contained within this fragment. To facilitate cloning of the PCR product, the PCR primers may also contain restriction endonuclease sites found in the cloning region of a conditional knockout vector such as pKO3 (Link, et al 1997 J. Bacteriol. 179 (20): 6228-6237). Suitable sites include NotI, SalI, BamHI and SmaI. The rplT gene fragments are produced using standard PCR conditions including, but not limited to, those outlined in the manufacturers directions for the Hot Start Taq PCR kit (Qiagen, Inc., Valencia, CA). The PCR reactions will produce two fragments that can be fused together. Alternatively, crossover PCR can be used to generate a desired deletion in one step (Ho, S. N., et al 1989. Gene 77: 51-59, Horton, R. M., et al 1989. Gene 77: 61-68). The mutant allele thus produced is called a "null" allele because it cannot produce a functional gene product.

The mutant allele obtained from PCR amplification is cloned into the multiple cloning site of pKO3. Directional cloning of the *rplT* null allele is not necessary. The pKO3 vector has a temperature-sensitive origin of replication derived from pSC101. Therefore, clones are propagated at the permissive temperature of 30°C. The vector also contains two selectable marker genes: one that confers resistance to chloramphenicol and another, the *Bacillus subtilis sacB* gene, that allows for counter-selection on sucrose containing growth medium. Clones that contain vector DNA with the null allele inserted are confirmed by restriction endonuclease analysis and DNA sequence analysis of isolated plasmid DNA. The plasmid containing the *rplT* null allele insert is known as a knockout plasmid.

Once the knockout plasmid has been constructed and its sequence verified, it is transformed into a Rec<sup>+</sup> E. coli host cell. Transformation can be by any standard method such as electroporation. In some fraction of the transformed cells, plasmids will integrate into the E. coli chromosome by homologous recombination between the rplT null allele in the plasmid and the rplT gene in the chromosome. Transformant colonies in which such an event has occurred are readily selected by growth at the non-permissive temperature of 43°C and in the presence of choramphenicol. At this temperature, the plasmid will not replicate as an episome and will be lost from cells as they grow and divide. These cells are no longer resistant to chloramphenicol and will not grow when it is present. However, cells in which the knockout plasmid has integrated into the E. coli chromosome remain resistant to chloramphenicol and propagate.

Cells containing integrated knock-out plasmids are usually the result of a single crossover event that creates a tandem repeat of the mutant and native wild type alleles of rplT separated by the

vector sequences. A consequence of this is that rplT will still be expressed in these cells. In order to determine if the gene is essential for growth, the wild type copy must be removed. This is accomplished by selecting for plasmid excision, a process in which homologous recombination between the two alleles results in looping out of the plasmid sequences. Cells that have undergone such an excision event and have lost plasmid sequences including sacB gene are selected for by addition of sucrose to the medium. The sacB gene product converts sucrose to a toxic molecule. Thus counter selection with sucrose ensures that plasmid sequences are no longer present in the cell. Loss of plasmid sequences is further confirmed by testing for sensitivity to chloramphenicol (loss of the chloramphenicol resistance gene). The latter test is important because occasionally a mutation in the sacB gene can occur resulting in a loss of sacB function with no effect on plasmid replication (Link, et. al., 1997 J. Bacteriol. 179 (20): 6228-6237). These artifact clones retain plasmid sequences and are therefore still resistant to chloramphenicol.

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In the process of plasmid excision, one of the two rplT alleles is lost from the chromosome along with the plasmid DNA. In general, it is equally likely that the null allele or the wild type allele will be lost. Therefore, if the rplT gene is not essential, half of the clones obtained in this experiment will have the wild type allele on the chromosome and half will have the null allele. However, if the rplT gene is essential, cells containing the null allele will not be obtained as a single copy of the null allele would be lethal.

To determine the essentiality of rplT, a statistically significant number of the resulting clones, at least 20, are analyzed by PCR amplification of the rplT gene. Since the null allele is missing a significant portion of the rplT gene, its PCR product is significantly shorter than that of the wild type gene and the two are readily distinguished by gel electrophoretic analysis. The PCR products may also be subjected to sequence determination for further confirmation by methods well known to those in the art.

The above experiment is generally adequate for determining the essentiality of a gene such as rplT. However, it may be necessary or desirable to more directly confirm the essentiality of the gene. There are several methods by which this can be accomplished. In general, these involve three steps: 1) construction of an episome containing a wild type allele, 2) isolation of clones containing a single chromosomal copy of the mutant null allele as described above but in the presence of the episomal wild type allele, and then 3) determining if the cells survive when the expression of the episomal allele is shut off. In this case, the trans copy of wild type rplT is made by PCR cloning of the entire coding region of rplT and inserting it in the sense orientation downstream of an inducible promoter such as the E. coli lac promoter. Transcription of this allele of rplT will be induced in the presence of IPTG which inactivates the lac repressor. Under IPTG induction rplT protein will be expressed as long as the recombinant gene also possesses a ribosomal binding site, also known as a "Shine-Dalgamo Sequence". The trans copy of rplT is cloned on a plasmid that is compatible with pSC101. Compatible vectors include p15A, pBR322, and the pUC

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plasmids, among others. Replication of the compatible plasmid will not be temperature-sensitive. The entire process of integrating the null allele of rplT and subsequent plasmid excision is carried out in the presence of IPTG to ensure the expression of functional rplT protein is maintained throughout. After the null rplT allele is confirmed as integrated on the chromosome in place of the wild type rplT allele, then IPTG is withdrawn and expression of functional rplT protein shut off. If the rplT gene is essential, cells will cease to proliferate under these conditions. However, if the rplT gene is not essential, cells will continue to proliferate under these conditions. In this experiment, essentiality is determined by conditional expression of a wild type copy of the gene rather than inability to obtain the intended chromosomal disruption.

An advantage of this method over some other gene disruption techniques is that the targeted gene can be deleted or mutated without the introduction of large segments of foreign DNA. Therefore, polar effects on downstream genes are eliminated or minimized. There are methods described to introduce inducible promoters upstream of potential essential bacterial genes. However in such cases, polarity from multiple transcription start points can be a problem. One way of preventing this is to insert a gene disruption cassette that contains strong transcriptional terminators upstream of the integrated inducible promoter (Zhang, Y, and Cronan, J. E. 1996 J. Bacteriol. 178 (12): 3614-3620). The described techniques will all be familiar to one of ordinary skill in the art.

Following the analysis of the *rplT* gene, the other genes of the operon are investigated to determine if they are required for proliferation.

#### **EXAMPLE 6**

#### Expression of the Proteins Encoded by Genes Identified as Required for E. coli Proliferation

The following is provided as one exemplary method to express the proliferation-required proteins encoded by the identified sequences described above. First, the initiation and termination codons for the gene are identified. If desired, methods for improving translation or expression of the protein are well known in the art. For example, if the nucleic acid encoding the polypeptide to be expressed lacks a methionine codon to serve as the initiation site, a strong Shine-Delgamo sequence, or a stop codon, these sequences can be added. Similarly, if the identified nucleic acid sequence lacks a transcription termination signal, this sequence can be added to the construct by, for example, splicing out such a sequence from an appropriate donor sequence. In addition, the coding sequence may be operably linked to a strong promoter or an inducible promoter if desired. The identified nucleic acid sequence or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial expression vector or genome using oligonucleotide primers complementary to the identified nucleic acid sequence or portion thereof and containing restriction endonuclease sequences for *Ncol* incorporated into the 5' primer and *Bgl*II at the 5' end of the corresponding 3'-primer, taking care to ensure that the identified nucleic acid sequence is positioned in frame with the termination signal. The

purified fragment obtained from the resulting PCR reaction is digested with NcoI and Bg/II, purified and ligated to an expression vector.

The ligated product is transformed into DH5 $\alpha$  or some other *E. coli* strain suitable for the over expression of potential proteins. Transformation protocols are well known in the art. For example, transformation protocols are described in: Current Protocols in Molecular Biology, Vol. 1, Unit 1.8, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Positive transformants are selected after growing the transformed cells on plates containing 50-100 µg/ml Ampicillin (Sigma, St. Louis, Missouri). In one embodiment, the expressed protein is held in the cytoplasm of the host organism. In an alternate embodiment, the expressed protein is released into the culture medium. In still another alternative, the expressed protein can be sequestered in the periplasmic space and liberated therefrom using any one of a number of cell lysis techniques known in the art. For example, the osmotic shock cell lysis method described in Chapter 16 of Current Protocols in Molecular Biology, Vol. 2, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Each of these procedures can be used to express a proliferation-required protein.

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Expressed proteins, whether in the culture medium or liberated from the periplasmic space or the cytoplasm, are then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, standard chromatography, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and HPLC. Alternatively, the secreted protein can be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment. The purity of the protein product obtained can be assessed using techniques such as Coomassie or silver staining or using antibodies against the control protein. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest can be generated using synthetic peptides using methods well known in the art. See, Antibodies: A Laboratory Manual, (Harlow and Lane, Eds.) Cold Spring Harbor Laboratory (1988). For example, 15-mer peptides having a sequence encoded by the appropriate identified gene sequence of interest or portion thereof can be chemically synthesized. The synthetic peptides are injected into mice to generate antibodies to the polypeptide encoded by the identified nucleic acid sequence of interest or portion thereof. Alternatively, samples of the protein expressed from the expression vectors discussed above can be purified and subjected to amino acid sequencing analysis to confirm the identity of the recombinantly expressed protein and subsequently used to raise antibodies. An Example describing in detail the generation of monoclonal and polyclonal antibodies appears in Example 7.

The protein encoded by the identified nucleic acid sequence of interest or portion thereof can be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted

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protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques. These procedures are well known in the art.

In an alternative protein purification scheme, the identified nucleic acid sequence of interest or portion thereof can be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the identified nucleic acid sequence of interest or portion thereof is inserted in-frame with the gene encoding the other half of the chimera. The other half of the chimera can be maltose binding protein (MBP) or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to MBP or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites can be engineered between the MBP gene or the nickel binding polypeptide and the identified expected gene of interest, or portion thereof. Thus, the two polypeptides of the chimera can be separated from one another by protease digestion.

One useful expression vector for generating maltose binding protein fusion proteins is pMAL (New England Biolabs), which encodes the *malE* gene. In the pMal protein fusion system, the cloned gene is inserted into a pMal vector downstream from the *malE* gene. This results in the expression of an MBP-fusion protein. The fusion protein is purified by affinity chromatography. These techniques as described are well known to those skilled in the art of molecular biology.

## **EXAMPLE 7**

# Production of an Antibody to an isolated E. coli Protein

Substantially pure protein or polypeptide is isolated from the transformed cells as described in Example 6. The concentration of protein in the final preparation is adjusted, for example, by concentration on a 10,000 molecular weight cut off AMICON filter device (Millipore, Bedförd, MA), to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

# Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or any of the well-known derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as ELISA, as described by Engvall, E., "Enzyme immunoassay ELISA and EMIT," Meth.

Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

# Polyclonal Antibody Production by Immunization

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Polyclonal antiserum containing antibodies to heterogeneous epitopes of a single protein or a peptide can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than larger molecules and can require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: **Handbook of Experimental Immunology** D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: **Manual of Clinical Immunology**, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies can also be used in therapeutic compositions for killing bacterial cells expressing the protein.

# **EXAMPLE 8**

# Screening Chemical Libraries

## A. Protein-Based Assays

Having isolated and expressed bacterial proteins shown to be required for bacterial proliferation, the present invention further contemplates the use of these expressed proteins in assays to screen libraries of compounds for potential drug candidates. The generation of chemical libraries is well known in the art. For example combinatorial chemistry can be used to generate a library of compounds to be screened in the assays described herein. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological

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synthesis by combining a number of chemical "building blocks" reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining amino acids in every possible combination to yield peptides of a given length. Millions of chemical compounds theoretically can be synthesized through such combinatorial mixings of chemical building blocks. For example, one commentator observed that the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery, Background and Peptide Combinatorial Libraries," Journal of Medicinal Chemistry, Vol. 37, No. 9, 1233-1250 (1994). Other chemical libraries known to those in the art may also be used, including natural product libraries.

Once generated, combinatorial libraries can be screened for compounds that possess desirable biological properties. For example, compounds which may be useful as drugs or to develop drugs would likely have the ability to bind to the target protein identified, expressed and purified as discussed above. Further, if the identified target protein is an enzyme, candidate compounds would likely interfere with the enzymatic properties of the target protein. Any enzyme can be a target protein. For example, the enzymatic function of a target protein can be to serve as a protease, nuclease, phosphatase, dehydrogenase, transporter protein, transcriptional enzyme, and any other type of enzyme known or unknown. Thus, the present invention contemplates using the protein products described above to screen combinatorial and other chemical libraries.

Those in the art will appreciate that a number of techniques exist for characterizing target proteins in order to identify molecules useful for the discovery and development of therapeutics. For example, some techniques involve the generation and use of small peptides to probe and analyze target proteins both biochemically and genetically in order to identify and develop drug leads. Such techniques include the methods described in PCT publications No. WO9935494, WO9819162, WO9954728.

In another example, the target protein is a serine protease and the substrate of the enzyme is known. The present example is directed towards the analysis of libraries of compounds to identify compounds that function as inhibitors of the target enzyme. First, a library of small molecules is generated using methods of combinatorial library formation well known in the art. U.S. Patent NOs. 5,463,564 and 5,574, 656, to Agrafiotis, et al., entitled "System and Method of Automatically Generating Chemical Compound with Desired Properties," are two such teachings. Then the library compounds are screened to identify library compounds that possess desired structural and functional properties. U.S. Patent No. 5,684,711 also discusses a method for screening libraries.

To illustrate the screening process, the combined target and chemical compounds of the library are exposed to and permitted to interact with the purified enzyme. A labeled substrate is added to the incubation. The label on the substrate is such that a detectable signal is emitted from metabolized substrate molecules. The emission of this signal permits one to measure the effect of the combinatorial

library compounds on the enzymatic activity of target enzymes. The characteristics of each library compound is encoded so that compounds demonstrating activity against the enzyme can be analyzed and features common to the various compounds identified can be isolated and combined into future iterations of libraries.

Once a library of compounds is screened, subsequent libraries are generated using those chemical building blocks that possess the features shown in the first round of screen to have activity against the target enzyme. Using this method, subsequent iterations of candidate compounds will possess more and more of those structural and functional features required to inhibit the function of the target enzyme, until a group of enzyme inhibitors with high specificity for the enzyme can be found. These compounds can then be further tested for their safety and efficacy as antibiotics for use in mammals.

It will be readily appreciated that this particular screening methodology is exemplary only. Other methods are well known to those skilled in the art. For example, a wide variety of screening techniques are known for a large number of naturally-occurring targets when the biochemical function of the target protein is known.

## B. Cell Based Assays

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Current cell-based assays used to identify or to characterize compounds for drug discovery and development frequently depend on detecting the ability of a test compound to inhibit the activity of a target molecule located within a cell or located on the surface of a cell. Most often such target molecules are proteins such as enzymes, receptors and the like. However, target molecules may also include other molecules such as DNAs, lipids, carbohydrates and RNAs including messenger RNAs, ribosomal RNAs, tRNAs and the like. A number of highly sensitive cell-based assay methods are available to those of skill in the art to detect binding and interaction of test compounds with specific target molecules. However, these methods are generally not highly effective when the test compound binds to or otherwise interacts with its target molecule with moderate or low affinity. In addition, the target molecule may not be readily accessible to a test compound in solution, such as when the target molecule is located inside the cell or within a cellular compartment such as the periplasm of a bacterial cell. Thus, current cell-based assay methods are limited in that they are not effective in identifying or characterizing compounds that interact with their targets with moderate to low affinity or compounds that interact with targets that are not readily accessible.

Cell-based assays methods of the present invention have substantial advantages over current cell-based assays practiced in the art. These advantages derive from the use of sensitized cells in which the level or activity of a proliferation-required gene product (the target molecule) has been specifically reduced to the point where the presence or absence of its function becomes a rate-determining step for cellular proliferation. Bacterial, fungal, plant, or animal cells can all be used with the present method. Such sensitized cells become much more sensitive to compounds that are

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active against the affected target molecule. Thus, cell-based assays of the present invention are capable of detecting compounds exhibiting low or moderate potency against the target molecule of interest because such compounds are substantially more potent on sensitized cells than on non-sensitized cells. The affect may be such that a test compound may be two to several times more potent, at least 10 times more potent or even at least 100 times more potent when tested on the sensitized cells as compared to the non-sensitized cells.

Due in part to the increased appearance of antibiotic resistance in pathogenic microorganisms and to the significant side-effects associated with some currently used antibiotics, novel antibiotics acting at new targets are highly sought after in the art. Yet, another limitation in the current art related to cell-based assays is the problem of identifying hits against the same kinds of target molecules in the same limited set of biological pathways over and over again. This may occur when compounds acting at such new targets are discarded, ignored or fail to be detected because compounds acting at the "old" targets are encountered more frequently and are more potent than compounds acting at the new targets. As a result, the majority of antibiotics in use currently interact with a relatively small number of target molecules within an even more limited set of biological pathways.

The use of sensitized cells of the current invention provides a solution to the above problem in two ways. First, desired compounds acting at a target of interest, whether a new target or a previously known but poorly exploited target, can now be detected above the "noise" of compounds acting at the "old" targets due to the specific and substantial increase in potency of such desired compounds when tested on the sensitized cells of the current invention. Second, the methods used to sensitize cells to compounds acting at a target of interest may also sensitize these cells to compounds acting at other target molecules within the same biological pathway. For example, expression of an antisense molecule to a gene encoding a ribosomal protein is expected to sensitize the cell to compounds acting at that ribosomal protein and may also sensitize the cells to compounds acting at any of the ribosomal components (proteins or rRNA) or even to compounds acting at any target which is part of the protein synthesis pathway. Thus an important advantage of the present invention is the ability to reveal new targets and pathways that were previously not readily accessible to drug discovery methods.

Sensitized cells of the present invention are prepared by reducing the activity or level of a target molecule. The target molecule may be a gene product, such as an RNA or polypeptide produced from the proliferation-required nucleic acids described herein. Alternatively, the target may be a gene product such as an RNA or polypeptide which is produced form a sequence within the same operon as the proliferation-required nucleic acids described herein. In addition, the target may be an RNA or polypeptide in the same biological pathway as the proliferation-required nucleic acids described herein. Such biological pathways include, but are not limited to, enzymatic,

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biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such the cell wall.

Current methods employed in the arts of medicinal and combinatorial chemistries are able to make use of structure-activity relationship information derived from testing compounds in various biological assays including direct binding assays and cell-based assays. Occasionally compounds are directly identified in such assays that are sufficiently potent to be developed as drugs. More often, initial hit compounds exhibit moderate or low potency. Once a hit compound is identified with low or moderate potency, directed libraries of compounds are synthesized and tested in order to identify more potent leads. Generally these directed libraries are combinatorial chemical libraries consisting of compounds with structures related to the hit compound but containing systematic variations including additions, subtractions and substitutions of various structural features. When tested for activity against the target molecule, structural features are identified that either alone or in combination with other features enhance or reduce activity. This information is used to design subsequent directed libraries containing compounds with enhanced activity against the target molecule. After one or several iterations of this process, compounds with substantially increased activity against the target molecule are identified and may be further developed as drugs. This process is facilitated by use of the sensitized cells of the present invention since compounds acting at the selected targets exhibit increased potency in such cell-based assays, thus; more compounds can now be characterized providing more useful information than would be obtained otherwise.

Thus, it is now possible using cell-based assays of the present invention to identify or characterize compounds that previously would not have been readily identified or characterized including compounds that act at targets that previously were not readily exploited using cell-based assays. The process of evolving potent drug leads from initial hit compounds is also substantially improved by the cell-based assays of the present invention because, for the same number of test compounds, more structure-function relationship information is likely to be revealed.

The method of sensitizing a cell entails selecting a suitable gene or operon. A suitable gene or operon is one whose expression is required for the proliferation of the cell to be sensitized. The next step is to introduce into the cells to be sensitized, an antisense RNA capable of hybridizing to the suitable gene or operon or to the RNA encoded by the suitable gene or operon. Introduction of the antisense RNA can be in the form of an expression vector in which antisense RNA is produced under the control of an inducible promoter. The amount of antisense RNA produced is limited by varying the inducer concentration to which the cell is exposed and thereby varying the activity of the promoter driving transcription of the antisense RNA. Thus, cells are sensitized by exposing them to an inducer concentration that results in a sub-lethal level of antisense RNA expression.

In one embodiment of the cell-based assays, the identified exogenous *E. coli* nucleotide sequences of the present invention are used to inhibit the production of a proliferation-required

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protein. Expression vectors producing antisense RNA against identified genes required for proliferation are used to limit the concentration of a proliferation-required protein without severly inhibiting growth. To achieve that goal, a growth inhibition dose curve of inducer is calculated by plotting various doses of inducer against the corresponding growth inhibition caused by the antisense expression. From this curve, various percentages of antisense induced growth inhibition, from 1 to 100% can be determined. If the promoter contained in the expression vector contains a lac operator the transcription is regulated by lac repressor and expression from the promoer is inducible with IPTG. For example, the highest concentration of the inducer IPTG that does not reduce the growth rate (0% growth inhibition) can be predicted from the curve. Cellular proliferation can be monitored by growth medium turbidity via OD measurements. In another example, the concentration of inducer that reduces growth by 25% can be predicted from the curve. In still another example, a concentration of inducer that reduces growth by 50% can be calculated. Additional parameters such as colony forming units (cfu) can be used to measure cellular viability.

Cells to be assayed are exposed to the above-determined concentrations of inducer. The presence of the inducer at this sub-lethal concentration reduces the amount of the proliferation required gene product to a low amount in the cell that will limit but not prevent growth. Cells grown in the presence of this concentration of inducer are therefore specifically more sensitive to inhibitors of the proliferation-required protein or RNA of interest or to inhibitors of proteins or RNAs in the same biological pathway as the proliferation-required protein or RNA of interest but not to inhibitors of unrelated proteins or RNAs.

Cells pretreated with sub-inhibitory concentrations of inducer and thus containing a reduced amount of proliferation-required target gene product are then used to screen for compounds that reduce cell growth. The sub-lethal concentration of inducer may be any concentration consistent with the intended use of the assay to identify candidate compounds to which the cells are more sensitive. For example, the sub-lethal concentration of the inducer may be such that growth inhibition is at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60% at least about 75%, 90%, 95% or more. Cells which are pre-sensitized using the preceding method are more sensitive to inhibitors of the target protein because these cells contain less target protein to be inhibited than do wild-type cells.

In another embodiment of the cell based assays of the present invention, the level or activity of a proliferation required gene product is reduced using a mutation, such as a temperature sensitive mutation, in the proliferation-required sequence and an antisense nucleic acid against the proliferation-required sequence. Growing the cells at an intermediate temperature between the permissive and restrictive temperatures of the temperature sensitive mutant where the mutation is in a proliferation-required gene produces cells with reduced activity of the proliferation-required gene product. The antisense RNA directed against the proliferation-required sequence further reduces

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the activity of the proliferation required gene product. Drugs that may not have been found using either the temperature sensitive mutation or the antisense nucleic acid alone may be identified by determining whether cells in which expression of the antisense nucleic acid has been induced and which are grown at a temperature between the permissive temperature and the restrictive temperature are substantially more sensitive to a test compound than cells in which expression of the antisense nucleic acid has not been induced and which are grown at a permissive temperature. Also drugs found previously from either the antisense nucleic acid alone or the temperature sensitive mutation alone may have a different sensitivity profile when used in cells combining the two approaches, and that sensitivity profile may indicate a more specific action of the drug in inhibiting one or more activities of the gene product.

Temperature sensitive mutations may be located at different sites within the gene and correspond to different domains of the protein. For example, the dnaB gene of Escherichia coli encodes the replication fork DNA helicase. DnaB has several domains, including domains for oligomerization, ATP hydrolysis, DNA binding, interaction with primase, interaction with DnaC, and interaction with DnaA [(Biswas, E.E. and Biswas, S.B. 1999. Mechanism and DnaB helicase of Escherichia coli: structural domains involved in ATP hydrolysis, DNA binding, and oligomerization. Biochem. 38:10919-10928; Hiasa, H. and Marians, K.J. 1999. Initiation of bidirectional replication at the chromosomal origin is directed by the interaction between helicase and primase. J. Biol. Chem. 274:27244-27248; San Martin, C., Radermacher, M., Wolpensinger, B., Engel, A., Miles, C.S., Dixon, N.E., and Carazo, J.M. 1998. Three-dimensional reconstructions from cryoelectron microscopy images reveal an intimate complex between helicase DnaB and its loading partner DnaC. Structure 6:501-9; Sutton, M.D., Carr, K.M., Vicente, M., and Kaguni, J.M. 1998. Escherichia coli DnaA protein. The N-terminal domain and loading of DnaB helicase at the E. coli chromosomal. J. Biol. Chem. 273:34255-62.)]. Temperature sensitive mutations in different domains of DnaB confer different phenotypes at the restrictive temperature, which include either an abrupt stop or slow stop in DNA replication with or without DNA breakdown (Wechsler, J.A. and Gross, J.D. 1971. Escherichia coli mutants temperature-sensitive for DNA synthesis. Mol. Gen. Genetics 113:273-284) and termination of growth or cell death. Combining the use of temperature sensitive mutations in the dnaB gene that cause cell death at the restrictive temperature with an antisense to the dnaB gene could lead to the discovery of very specific and effective inhibitors of one or a subset of activities exhibited by DnaB.

When screening for antimicrobial agents against a gene product required for proliferation, growth inhibition of cells containing a limiting amount of that proliferation-required gene product can be assayed. Growth inhibition can be measured by directly comparing the amount of growth, measured by the optical density of the growth medium, between an experimental sample and a control sample. Alternative methods for assaying cell proliferation include measuring green

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fluorescent protein (GFP) reporter construct emissions, various enzymatic activity assays, and other methods well known in the art.

It will be appreciated that the above method may be performed in solid phase, liquid phase or a combination of the two. For example, cells grown on nutrient agar containing the inducer of the antisense construct may be exposed to compounds spotted onto the agar surface. A compound's effect may be judged from the diameter of the resulting killing zone, the area around the compound application point in which cells do not grow. Multiple compounds may be transferred to agar plates and simultaneously tested using automated and semi-automated equipment including but not restricted to multi-channel pipettes (for example the Beckman Multimek) and multi-channel spotters (for example the Genomic Solutions Flexys). In this way multiple plates and thousands to millions of compounds may be tested per day.

The compounds may also be tested entirely in liquid phase using microtiter plates as described below. Liquid phase screening may be performed in microtiter plates containing 96, 384, 1536 or more wells per microtiter plate to screen multiple plates and thousands to millions of compounds per day. Automated and semi-automated equipment may be used for addition of reagents (for example cells and compounds) and determination of cell density.

#### **EXAMPLE 9**

Cell Based Assay Using Antisense Complementary to Genes Encoding Ribosomal Proteins

The effectiveness of the above cell based assay was validated using constructs expressing antisense RNA to the proliferation required E. coli genes rplL, rplJ, and rplW encoding ribosomal proteins L7/L12, L10 and L23 respectively. These proteins are part of the protein synthesis apparatus of the cell and as such are required for proliferation. These constructs were used to test the effect of antisense expression on cell sensitivity to antibiotics known to bind to the ribosome and thereby inhibit protein synthesis. Constructs expressing antisense RNA to several other genes (elaD, visC, yohH, and atpE/B), the products of which are not involved in protein synthesis were used for comparison.

First pLex5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)) expression vectors containing antisense constructs to either *rplW* or to *elaD* were introduced into separate *E. coli* cell populations. Vector introduction is a technique well known to those of ordinary skill in the art. The expression vectors of this example contain IPTG inducible promoters that drive the expression of the antisense RNA in the presence of the inducer. However, those skilled in the art will appreciate that other inducible promoters may also be used. Suitable expression vectors are also well known in the art. The *E. coli* antisense clones encoding ribosomal proteins L7/L12, L10 and L23 were used to test the effect of antisense expression on cell sensitivity to the antibiotics known to bind to these proteins. First, expression vectors containing antisense to either the genes encoding L7/L12 and L10 or L23 were introduced into separate *E. coli* cell populations.

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The cell populations were exposed to a range of IPTG concentrations in liquid medium to obtain the growth inhibitory dose curve for each clone (Fig. 1). First, seed cultures were grown to a particular turbidity that is measured by the optical density (OD) of the growth solution. The OD of the solution is directly related to the number of bacterial cells contained therein. Subsequently, sixteen 200 ul liquid medium cultures were grown in a 96 well microtiter plate at 37 C with a range of IPTG concentrations in duplicate two-fold serial dilutions from 1600 uM to 12.5 uM (final concentration). Additionally, control cells were grown in duplicate without IPTG. These cultures were started from equal amounts of cells derived from the same initial seed culture of a clone of interest. The cells were grown for up to 15 hours and the extent of growth was determined by measuring the optical density of the cultures at 600 nm. When the control culture reached mid-log phase the percent growth of the control for each of the IPTG containing cultures was plotted against the log concentrations of IPTG to produce a growth inhibitory dose response curve for the IPTG. The concentration of IPTG that inhibits cell growth to 50% (IC<sub>50</sub>) as compared to the 0 mM IPTG control (0% growth inhibition) was then calculated from the curve. Under these conditions, an amount of antisense RNA was produced that reduced the expression levels of rplW and elaD to a degree such that growth was inhibited by 50%.

Alternative methods of measuring growth are also contemplated. Examples of these methods include measurements of proteins, the expression of which is engineered into the cells being tested and can readily be measured. Examples of such proteins include green fluorescent protein (GFP) and various enzymes.

Cells were pretreated with the selected concentration of IPTG and then used to test the sensitivity of cell populations to tetracycline, erythromycin and other protein synthesis inhibitors. Figure 2 is an IPTG dose response curve in E. coli transformed with an IPTG-inducible plasmid containing either an antisense clone to the E. coli ribosomal protein rplW (AS-rplW) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the elaD (AS-elaD) gene which is not known to be involved in protein synthesis and which is also essential An example of a tetracycline dose response curve is for proliferation. shown in Figures 2A and 2B for the rplW and elaD genes, respectively. Cells were grown to log phase and then diluted into media alone or media containing IPTG at concentrations which give 20% and 50% growth inhibition as determined by IPTG dose response curves. After 2.5 hours, the cells were diluted to a final OD600 of 0.002 into 96 well plates containing (1) +/- IPTG at the same concentrations used for the 2.5 hour pre-incubation; and (2) serial two-fold dilutions of tetracycline such that the final concentrations of tetracycline range from 1 µg/ml to 15.6 ng/ml and 0 µg/ml. The 96 well plates were incubated at 37°C and the OD600 was read by a plate reader every 5 minutes for up to 15 hours. For each IPTG concentration and the no IPTG control, tetracycline dose response curves were determined when the control (absence of tetracycline) reached 0.1 OD600. To compare tetracycline sensitivity with and without IPTG, tetracycline IC50s were

determined from the dose response curves (Figs. 3A-B). Cells with reduced levels of L23 (rplW) showed increased sensitivity to tetracycline (Fig. 2A) as compared to cells with reduced levels of elaD (Fig. 2B). Figure 3 shows a summary bar chart in which the ratios of tetracycline IC<sub>50s</sub> determined in the presence of IPTG which gives 50% growth inhibition versus tetracycline IC<sub>50s</sub> determined without IPTG (fold increase in tetracycline sensitivity) were plotted. Cells with reduced levels of either L7/L12 (genes rplL, rplJ) or L23 (rplW) showed increased sensitivity to tetracycline (Fig. 3). Cells expressing antisense to genes not known to be involved in protein synthesis (atpB/E, visC, elaD, yohH) did not show the same increased sensitivity to tetracycline, validating the specificity of this assay (Fig. 3).

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In addition to the above, it has been observed in initial experiments that clones expressing antisense RNA to genes involved in protein synthesis (including genes encoding ribosomal proteins L7/L12 & L10, L7/L12 alone, L22, and L18, as well as genes encoding rRNA and Elongation Factor G) have increased sensitivity to the macrolide, erythromycin, whereas clones expressing antisense to the non-protein synthesis genes *elaD*, *atpB/E* and *visC* do not. Furthermore, the clone expressing antisense to *rplL* and *rplJ* does not show increased sensitivity to nalidixic acid and ofloxacin, antibiotics which do not inhibit protein synthesis.

The results with the ribosomal protein genes rplL, rplJ, and rplW as well as the initial results using various other antisense clones and antibiotics show that limiting the concentration of an antibiotic target makes cells more sensitive to the antimicrobial agents that specifically interact with that protein. The results also show that these cells are sensitized to antimicrobial agents that inhibit the overall function in which the protein target is involved but are not sensitized to antimicrobial agents that inhibit other functions.

The cell based assay described above may also be used to identify the biological pathway in which a proliferation-required nucleic acid or its gene product lies. In such methods, cells expressing a sub-lethal level of antisense to a target proliferation-required nucleic acid and control cells in which expression of the antisense has not been induced are contacted with a panel of antibiotics known to act in various pathways. If the antibiotic acts in the pathway in which the target proliferation-required nucleic acid or its gene product lies, cells in which expression of the antisense has been induced will be more sensitive to the antibiotic than cells in which expression of the antisense has not been induced.

As a control, the results of the assay may be confirmed by contacting a panel of cells expressing antisense nucleic acids to many different proliferation-required genes including the target proliferation-required gene. If the antibiotic is acting specifically, heightened sensitivity to the antibiotic will be observed only in the cells expressing antisense to a target proliferation-required gene (or cells expressing antisense to other proliferation-required genes in the same pathway as the target proliferation-required gene) but will not be observed generally in all cells expressing antisense to proliferation-required genes.

Similarly, the above method may be used to determine the pathway on which a test compound, such as a test antibiotic acts. A panel of cells, each of which expresses antisense to a proliferation-required nucleic acid in a known pathway, is contacted with a compound for which it is desired to determine the pathway on which it acts. The sensitivity of the panel of cells to the test compound is determined in cells in which expression of the antisense has been induced and in control cells in which expression of the antisense has not been induced. If the test compound acts on the pathway on which an antisense nucleic acid acts, cells in which expression of the antisense has been induced will be more sensitive to the compound than cells in which expression of the antisense has not been induced. In addition, control cells in which expression of antisense to proliferation-required genes in other pathways has been induced will not exhibit heightened sensitivity to the compound. In this way, the pathway on which the test compound acts may be determined.

The Example below provides one method for performing such assays.

#### **EXAMPLE 10**

Identification of the Pathway in which a Proliferation-Required

Gene Lies or the Pathway on which an Antibiotic Acts

# A. Preparation of Bacterial Stocks for Assay

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To provide a consistent source of cells to screen, frozen stocks of host bacteria containing the desired antisense construct are prepared using standard microbiological techniques. For example, a single clone of the organism can be isolated by streaking out a sample of the original stock onto an agar plate containing nutrients for cell growth and an antibiotic for which the antisense construct contains a gene which confers resistance. After overnight growth an isolated colony is picked from the plate with a sterile needle and transferred to an appropriate liquid growth media containing the antibiotic required for maintenance of the plasmid. The cells are incubated at 30°C to 37°C with vigorous shaking for 4 to 6 hours to yield a culture in exponential growth. Sterile glycerol is added to 15% (volume to volume) and 100µL to 500 µL aliquots are distributed into sterile cryotubes, snap frozen in liquid nitrogen, and stored at -80°C for future assays.

# B. Growth of Bacteria for Use in the Assay

A day prior to an assay, a stock vial is removed from the freezer, rapidly thawed (37°C water bath) and a loop of culture is streaked out on an agar plate containing nutrients for cell growth and an antibiotic to which the antisense construct confers resistance. After overnight growth at 37°C, ten randomly chosen, isolated colonies are transferred from the plate (sterile inoculum loop) to a sterile tube containing 5 mL of LB medium containing the antibiotic to which the antisense vector confers resistance. After vigorous mixing to form a homogeneous cell suspension, the optical density of the suspension is measured at 600 nm (OD600) and if necessary an aliquot of the suspension is diluted into a second tube of 5 mL, sterile, LB medium plus antibiotic to achieve an

 $OD600 \le 0.02$  absorbance units. The culture is then incubated at 37° C for 1-2 hrs with shaking until the OD600 reaches OD 0.2 – 0.3. At this point the cells are ready to be used in the assay.

#### 5 C. Selection of Media to be Used in Assay

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Two fold dilution series of the inducer are generated in culture media containing the appropriate antibiotic for maintenance of the antisense construct. Several media are tested side by side and three to four wells are used to evaluate the effects of the inducer at each concentration in each media. For example, M9 minimal media, LB broth, TBD broth and Muller-Hinton media may be tested with the inducer IPTG at the following concentrations, 50 µM, 100 µM, 200 µM, 400 µM, 600 µM, 800 µM and 1000 µM. Equal volumes of test media-inducer and cells are added to the wells of a 384 well microtiter plate and mixed. The cells are prepared as described above and diluted 1:100 in the appropriate media containing the test antibiotic immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells of each media that do not contain inducer, for example 0 µM IPTG. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of inducer is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without inducer. The medium yielding greatest sensitivity to inducer is selected for use in the assays described below.

#### D. Measurement of Test Antibiotic Sensitivity in the Absence of Antisense Construct Induction

Two-fold dilution series of antibiotics of known mechanism of action are generated in the culture media selected for further assay development that has been supplemented with the antibiotic used to maintain the construct. A panel of test antibiotics known to act on different pathways is tested side by side with three to four wells being used to evaluate the effect of a test antibiotic on cell growth at each concentration. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the media selected for assay development supplemented with the antibiotic required to maintain the antisense construct and are diluted 1:100 in identical media immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells that contain the solvent used to dissolve the antibiotics but no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC50 value for each antibiotic.

# E. Measurement of Test Antibiotic Sensitivity in the Presence of Antisense Construct Inducer

The culture media selected for use in the assay is supplemented with inducer at concentrations shown to inhibit cell growth by 50 and 80% as described above and the antibiotic used to maintain the construct. Two fold dilution series of the panel of test antibiotics used above are generated in each of these media. Several antibiotics are tested side by side with three to four wells being used to evaluate the effects of an antibiotic on cell growth at each concentration, in each media. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter. plate and mixed. Cells are prepared as described above using the media selected for use in the assay supplemented with the antibiotic required to maintain the antisense construct. The cells are diluted 1:100 into two 50 mL aliquots of identical media containing concentrations of inducer that have been shown to inhibit cell growth by 50% and 80 % respectively and incubated at 37°C with shaking for 2.5 hours. Immediately prior to addition to the microtiter plate wells, the cultures are adjusted to an appropriate OD<sub>600</sub> (typically 0.002) by dilution into warm (37°C) sterile media supplemented with identical concentrations of the inducer and antibiotic used to maintain the antisense construct. For a control, cells are also added to several wells that contain solvent used to dissolve test antibiotics but which contain no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC<sub>50</sub> value for each antibiotic.

## F. Determining the Specificity of the Test Antibiotics

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A comparison of the IC<sub>50</sub>s generated by antibiotics of known mechanism of action under antisense induced and non-induced conditions allows the pathway in which a proliferation-required nucleic acid lies to be identified. If cells expressing an antisense nucleic acid against a proliferation-required gene are selectively sensitive to an antibiotic acting via a particular pathway, then the gene against which the antisense acts is involved in the pathway in which the antibiotic acts.

## G. Identification of Pathway in which a Test Antibiotic Acts

As discussed above, the cell based assay may also be used to determine the pathway against which a test antibiotic acts. In such an analysis, the pathways against which each member of a panel of antisense nucleic acids acts are identified as described above. A panel of cells, each containing an inducible antisense vector against a gene in a known proliferation-required pathway, is contacted with a test antibiotic for which it is desired to determine the pathway on which it acts under inducing an non-inducing conditions. If heightened sensitivity is observed in induced cells expressing antisense against a gene in a particular pathway but not in induced cells expressing

antisense against genes in other pathways, then the test antibiotic acts against the pathway for which heightened sensitivity was observed.

One skilled in the art will appreciate that further optimization of the assay conditions, such as the concentration of inducer used to induce antisense expression and/or the growth conditions used for the assay (for example incubation temperature and media components) may further increase the selectivity and/or magnitude of the antibiotic sensitization exhibited.

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The following example confirms the effectiveness of the methods described above.

#### **EXAMPLE 11**

# Identification of the Pathway in which a Proliferation-Required Gene Lies

Antibiotics of various chemical classes and modes of action were purchased from Sigma Chemicals (St. Louis, MO). Stock solutions were prepared by dissolving each antibiotic in an appropriate aqueous solution based on information provided by the manufacturer. The final working solution of each antibiotic contained no more than 0.2% (w/v) of any organic solvent. To determine their potency against a bacterial strain engineered for expression of an antisense against a proliferation-required gene encoding 50S ribosomal protein, each antibiotic was serially diluted two or three fold in growth medium supplemented with the appropriate antibiotic for maintenance of the anti-sense construct. At least ten dilutions were prepared for each antibiotic. 25 µL aliquots of each dilution were transferred to discrete wells of a 384-well microplate (the assay plate) using a multichannel pipette. Quadruplicate wells were used for each dilution of an antibiotic under each treatment condition (plus and minus inducer). Each assay plate contained twenty wells for cell growth controls (growth media replacing antibiotic), ten wells for each treatment (plus and minus inducer, in this example IPTG). Assay plates were usually divided into the two treatments: half the plate containing induced cells and an appropriate concentrations of inducer (in this example IPTG) to maintain the state of induction, the other half containing non-induced cells in the absence of IPTG.

Cells for the assay were prepared as follows. Bacterial cells containing a construct, from which expression of antisense nucleic acid against rplL and rplJ, which encode proliferation-required 50S ribosomal subunit proteins, is inducible in the presence of IPTG, were grown into exponential growth (OD<sub>600</sub> 0.2 to 0.3) and then diluted 1:100 into fresh media containing either 400  $\mu$ M or 0  $\mu$ M inducer (IPTG). These cultures were incubated at 37° C for 2.5 hr. After a 2.5 hr incubation, induced and non-induced cells were respectively diluted into an assay medium at a final OD<sub>600</sub> value of 0.0004. The medium contained an appropriate concentration of the antibiotic for the maintenance of the anti-sense construct. In addition, the medium used to dilute induced cells was supplemented with 800  $\mu$ M IPTG so that addition to the assay plate would result in a final IPTG concentration of 400  $\mu$ M. Induced and non-induced cell suspensions were dispensed (25  $\mu$ l/well) into the appropriate wells of the assay plate as discussed previously. The plate was then loaded into

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a plate reader, incubated at constant temperature, and cell growth was monitored in each well by the measurement of light scattering at 595 nm. Growth was monitored every 5 minutes until the cell culture attained a stationary growth phase. For each concentration of antibiotic, a percentage inhibition of growth was calculated at the time point corresponding to mid-exponential growth for the associated control wells (no antibiotic, plus or minus IPTG). For each antibiotic and condition (plus or minus IPTG), a plot of percent inhibition versus log of antibiotic concentration was generated and the IC50 determined. A comparison of the IC<sub>50</sub> for each antibiotic in the presence and absence of IPTG revealed whether induction of the antisense construct sensitized the cell to the mechanism of action exhibited by the antibiotic. Cells which exhibited a significant (standard statistical analysis) numerical decrease in the IC<sub>50</sub> value in the presence of inducer were considered to have an increased sensitivity to the test antibiotic.

The results are provided in the table below, which lists the classes and names of the antibiotics used in the analysis, the targets of the antibiotics, the IC50 in the absence of IPTG, the IC50 in the presence of IPTG, the concentration units for the IC50s, the fold increase in IC50 in the presence of IPTG, and whether increased sensitivity was observed in the presence of IPTG.

TABLE IV

Effect of Expression of Antisense RNA to rplL and rplJ on Antibiotic Sensitivity

ANTIBIOTIC CLASS /Names	TARGET	ICSO (-IPTG)	CSO (+IPTG)	Conc.	ICS0 (-IPTG) ICS0 (+IPTG) Conc. Fold Increase Sensitivity	Sensitivity
				Unit	in Sensitivity Increased?	Increased?
PROTEIN SYNTHESIS INHIBITOR						
ANTIBIOTICS						
AMINOGLYCOSIDES						
Gentamicin	30S ribosome function	2715	19.19	ng/ml	141	Yes
Streptomycin	30S ribosome function	11280	161	ng/ml	2	Yes
Spectinomycin	30S ribosome function	18050	<156	ng/ml		Yes
Tobramycin	30S ribosome function	3594	70.58	lm/gu	51	Yes
MACROLIDES						
Erythromycin	50S ribosome function	7467	187	ng/ml	40	Yes
AROMATIC POYKETIDES		•				
Tetracycline	30S ribosome function	199.7	1.83	ng/ml	601	Yes
Minocycline	30S ribosome function	668.4	3.897	ng/ml	172	Yes
Doxycycline	30S ribosome function	413.1	27.81	ng/ml	15	Yes
OTHER PROTEIN SYNTHESIS INHIBITORS						
Fusidic acid	Elongation Factor G function	29990	641	ng/ml	8	Yes
Chloramphenicol	30S ribosome function	465.4	1.516	ng/ml	307	Yes
Lincomycin	50S ribosome function	47150	324.2	ng/ml	145	Yes

ANTIBIOTIC CLASS /Names	TARGET	(ST41-) 0SOI	ICSO (+IPTG)	Conc	ICS0 (-IPTG) ICS0 (+IPTG) Conc. Fold Increase Sensitivity	Sensitivity
				Unit	in Sensitivity Increased?	Increased?
OTHER ANTIBIOTIC MECHANISMS						
B-LACTAMS						
Cefoxitin	Cell wall biosynthesis	2782	2484	ng/ml	-	N <sub>0</sub>
Cefotaxime	Cell wall biosynthesis	24.3	24.16	ng/ml	-	N <sub>o</sub>
DNA SYNTHESIS INHIBITORS	•					
Nalidixic acid	DNA Gyrase activity	6973	6025	ng/ml	-	%
Ofloxacin	DNA Gyrase activity	49.61	45.89	ng/ml	-	ž
ОТНЕК	,					
Bacitracin	Cell membrane function	4077	4677	mg/ml	-	Š
Trimethoprim	Dihydrofolate Reductase activity	128.9	181.97	ng/ml	_	8 N
Vancomycin	Cell wall biosynthesis	145400	72550	ng/ml	2	No

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The above results demonstrate that induction of an antisense RNA to genes encoding 50S ribosomal subunit proteins results in a selective and highly significant sensitization of cells to antibiotics that inhibit ribosomal function and protein synthesis. The above results further demonstrate that induction of an antisense construct to an essential gene sensitizes an organism to compounds that interfere with that gene products' biological role. This sensitization is restricted to compounds that interfere with pathways associated with the targeted gene and it's product.

Assays utilizing antisense constructs to essential genes can be used to identify compounds that specifically interfere with the activity of multiple targets in a pathway. Such constructs can be used to simultaneously screen a sample against multiple targets in one pathway in one reaction (Combinatorial HTS).

Furthermore, as discussed above, panels of antisense construct containing cells may be used to characterize the point of intervention of any compound affecting an essential biological pathway including antibiotics with no known mechanism of action.

Another embodiment of the present invention is a method for determining the pathway against which a test antibiotic compound is active in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for determining which pathway a test antibiotic acts against except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required gene product is reduced using sublethal level of a known antibiotic which acts against the proliferation required gene product.

Interactions between drugs which affect the same biological pathway has been described in the literature. For example, Mecillinam (Amdinocillin) binds to and inactivates the penicillin binding protein 2 (PBP2, product of the *mrdA* in *E. coli*). This antibiotic inteacts with other antibiotics that inhibit PBP2 as well as antibiotics that inhibit other penicillin binding proteins such as PBP3 [(Gutmann, L., Vincent, S., Billot-Klein, D., Acar, J.F., Mrena, E., and Williamson, R. (1986) Involvement of penicillin-binding protein 2 with other penicillin-binding proteins in lysis of *Escherichia coli* by some beta-lactam antibiotics alone and in synergistic lytic effect of amdinocillin (mecillinam). Antimicrobial Agents & Chemotherapy, 30:906-912)]. Interactions between drugs could, therefore, involve two drugs that inhibit the same target protein or nucleic acid or inhibit different proteins or nucleic acids in the same pathway [(Fukuoka, T., Domon, H., Kakuta, M., Ishii, C., Hirasawa, A., Utsui, Y., Ohya, S., and Yasuda, H. (1997) Combination effect

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between panipenem and vancomycin on highly methicillin-resistant Staphylococcus aureus. Japan. J. Antibio. 50:411-419; Smith, C.E., Foleno, B.E., Barrett, J.F., and Frosc, M.B. (1997) Assessment of the synergistic interactions of levofloxacin and ampicillin against Enterococcus faecium by the checkerboard agar dilution and time-kill methods. Diagnos. Microbiol. Infect. Disease 27:85-92; den Hollander, J.G., Horrevorts, A.M., van Goor, M.L., Verbrugh, H.A., and Mouton, J.W. (1997) Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. Antimicrobial Agents & Chemotherapy. 41:95-110)].

Two drugs may interact even though they inhibit different targets. For example, the proton pump inhibitor, Omeprazole, and the antibiotic, Amoxycillin, two synergistic compounds acting together, can cure *Helicobacter pylori* infection [( Gabryelewicz, A., Laszewicz, W., Dzieniszewski, J., Ciok, J., Marlicz, K., Bielecki, D., Popiela, T., Legutko, J., Knapik, Z., Poniewierka, E. (1997) Multicenter evaluation of dual-therapy (omeprazol and amoxycillin) for *Helicobacter pylori*-associated duodenal and gastric ulcer (two years of the observation). J. Physiol. Pharmacol. 48 Suppl 4:93-105)].

The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

Cells are contacted with a combination of each member of a panel of known antibiotics at a sublethal level and varying concentrations of the test antibiotic. As a control, the cells are contacted with varying concentrations of the test antibiotic alone. The IC<sub>50</sub> of the test antibiotic in the presence and absence of the known antibiotic is determined. If the IC50s in the presence and absence of the known drug are substantially similar, then the test drug and the known drug act on different pathways. If the IC<sub>50</sub>s are substantially different, then the test drug and the known drug act on the same pathway.

Another embodiment of the present invention is a method for identifying a candidate compound for use as an antibiotic in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for identifying candidate compounds for use as antibiotics except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required

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gene product is reduced using a sublethal level of a known antibiotic which acts against the proliferation required gene product.

The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

In order to characterize test compounds of interest, cells are contacted with a panel of known antibiotics at a sublethal level and one or more concentrations of the test compound. As a control, the cells are contacted with the same concentrations of the test compound alone. The IC<sub>50</sub> of the test compound in the presence and absence of the known antibiotic is determined. If the IC<sub>50</sub> of the test compound is substantially different in the presence and absence of the known drug then the test compound is a good candidate for use as an antibiotic. As discussed above, once a candidate compound is identified using the above methods its structure may be optimized using standard techniques such as combinatorial chemistry.

Representative known antibiotics which may be used in each of the above methods are provided in the table below. However, it will be appreciated that other antibiotics may also be used.

ANTIBIOTIC	INHIBITS/TARGET	RESISTANT MUTANTS
Inhibitors of Transcription		
Rifamycin, 1959 Rifampicin Rifabutin Rifaximin	Inhibits initiation of transcription/B-subunit RNA polymerase, rpoB	rpoB, crp, cyaA
Streptolydigin	Accelerates transcription chain termination/B-subunit RNA polymerase	rpoB
Streptovaricin	an acyclic ansamycin, inhibits RNA polymerase	rpoB
Actinomycin D+EDTA	Intercalates between 2 successive G-C pairs, <i>rpoB</i> , inhibits RNA synthesis	pldA
Inhibitors of Nucleic Acid Me	tabolism	
Quinolones, 1962 Nalidixic acid Oxolinic acid	α subunit gyrase and/or topoisomerase IV, gyrA	gyrAorB, icd, sloB
Fluoroquinolones Ciprofloxacin, 1983 Norfloxacin	α subunit gyrase, gyrA and/or topoisomerase IV (probable target in Staph)	gyrA norA (efflux in Staph) hipQ
Coumerins Novobiocin	Inhibits ATPase activity of \( \beta\)-subunit gyrase, \( gyrB \)	gyrB, cysB, cysE, nov, ompA
Coumermycin	Inhibits ATPase activity of B-subunit gyrase, gyrB	gyrB, hisW
Albicidin	DNA synthesis	tsx (nucleoside channel)
Metronidazole	Causes single-strand breaks in DNA	nar

Inhibitors of Metabolic Pathways Sulfonamides, 1932 blocks synthesis of dihydrofolate, dihydrofolP, gpt, pabA, pabB, Sulfanilamide pteroate synthesis, folP pabC Inhibits dihydrofolate reductase, folA folA, thyA Trimethoprim, 1962 Nucleoside analogue capable of alkylating nupC, pnp Showdomycin sulfhydryl groups, inhibitor of thymidylate synthetase type II fatty acid synthase inhibitor Thiolactomycin fadB, emrB due to gene dosage **Psicofuranine** Adenosine glycoside antibiotic, target is guaA,B **GMP** synthetase Inhibits fatty acid synthesis fabl (envM) Triclosan Diazoborines Isoniazid, heterocyclic, contains boron, inhibit fatty fabl (envM) Ethionamide acid synthesis, enoyl-ACP reductase, fabl Inhibitors of Translation Phenylpropanoids Binds to ribosomal peptidyl transfer center Chloramphenicol, 1947 preventing peptide translocation/ binds to rrn, cmlA, marA, ompF, S6, L3, L6, L14, L16, L25, L26, L27, but ompRpreferentially to L16 Binding to 30S ribosomal subunit, "A" site Tetracyclines, 1948, type II clmA (cmr), mar, ompF on 30S subunit, blocks peptide elongation, polyketides Minocycline strongest binding to S7 Doxycycline Binding to 50 S ribosomal subunit, 23S Macrolides (type I polyketides) rRNA, blocks peptide translocation, L15, Erythromycin, 1950 Carbomycin, Spiramycin L4, L12 rrn, rplC, rplD, rplV, mac etc Irreversible binding to 30S ribosomal Aminoglycosides Streptomycin, rpsL, strC,M, ubiF subunit, prevents translation or causes 1944 mistranslation of mRNA/16S rRNA atpA-E, ecfB, Neomycin hemAC,D,E,G, topA, rpsC,D,E, rrn, spcB Spectinomycin atpA-atpE, cpxA, ecfB, hemA,B,L, topA Kanamycin ksgA,B,C,D, rplB,K, rpsI,N,M,R Kasugamycin rplF, ubiF cpxA Gentamicin, 1963 rpsL Amikacin Paromycin Lincosamides Binding to 50 S ribosomal subunit, blocks Lincomycin, 1955 peptide translocation linB, rplN,O, rpsG Clindamycin Streptogramins Virginiamycin, 2 components, Streptogramins A&B, bind 1955 Pristinamycin to the 50S ribosomal subunit blocking peptide translocation and peptide bond Synercid: quinupristin /dalfopristin formation Inhibition of elongation factor G (EF-G) **Fusidanes** fusA **Fusidic Acid** prevents peptide translocation Inhibition of elongation factor TU (EF-Tu), Kirromycin (Mocimycin) tufA,B prevents peptide bond formation Binds to and inhibits EF-TU Pulvomycin Sulfur-containing antibiotic, inhibits protein Thiopeptin rplEsynthesis.EF-G

**Tiamulin** Inhibits protein synthesis rplC, rplD Negamycin Inhibits termination process of protein prfB synthesis

Oxazolidinones Linezolid 23S rRNA

Nitrofurantoin

Isoniazid

convert nitrofurantoin to highly reactive electrophilic intermediates which attack bacterial ribosomal proteins non-

Inhibits protein synthesis, nitroreductases

specifically

Pseudomonic Acids Mupirocin Inhibition of isoleucyl tRNA synthetase-(Bactroban) used for Staph, topical cream, nasal

Indolmycin Inhibits tryptophanyl-tRNA synthetase

Viomycin

rrmA (23S rRNA methyltransferase; mutant has slow growth rate, slow chain elongation rate, and viomycin

pdx

ileS

trpS

nfnA,B

resistance) Thiopeptides Binds to L11-23S RNA complex

Inhibits GTP hydrolysis by EF-G

Stimulates GTP hydrolysis by EF-G Micrococcin

Inhibitors of Cell Walls/Membranes

Thiostrepton

**B-lactams** Inhibition of one or more cell wall Penicillin, 1929 Ampicillin transpeptidases, endopeptidases, and glycosidases (PBPs), of the 12 PBPs only 2 ampC, ampD, ampE, Methicillin, 1960 envZ, galU, hipA,

are essential: mrdA (PBP2) and ftsI (pbpB, hipQ, ompC, ompF, PBP3)

> ompR, ptsI, rfa, tolD, tolE

Cephalosporins, 1962 tonB

Binds to and inactivates PBP2 (mrdA) alaS, argS, crp, cyaA, Mecillinam (amdinocillin) envB, mrdA,B, Inactivates PBP3 (fts/) mreB,C,D

Aztreonam (Furazlocillin) Bacilysin, Tetaine Dipeptide, inhib glucosamine synthase dppA

Glycopeptides Vancomycin, 1955 Inhib G+ cell wall syn, binds to terminal D-ala-D-ala of pentapeptide,

Polypeptides Prevents dephosphorylation and **Bacitracin** regeneration of lipid carrier rfa

Cyclic lipopeptide Daptomycin, Disrupts multiple aspects of membrane 1980 function, including peptidoglycan

synthesis, lipoteichoic acid synthesis, and the bacterial membrane potential Cyclic polypeptides Polymixin, Surfactant action disrupts cell membrane pmrA

1939 lipids, binds lipid A mioety of LPS Fosfomycin, 1969 Analogue of P-enolpyruvate, inhibits 1st murA, crp, cyaA glpT,

step in peptidoglycan synthesis - UDP-NhipA, ptsI, uhpT acetylglucosamine enolpyruvyl

transferase, murA. Also acts as **Immunosuppressant** 

Cycloserine Prevents formation of D-ala dimer, hipA, cycA inhibits D-ala ligase, ddlA,B

Alafosfalin phosphonodipeptide, cell wall synthesis

phosphonodipeptide, cell wall synthesis pepA, tpp inhibitor, potentiator of  $\beta$ -lactams

Ipp. dnaE

Inhibitors of Protein Processing/Transport

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Globomycin Inhibits signal peptidase II (cleaves

prolipoproteins subsequent to lipid

modification, lspA

#### **EXAMPLE 12**

Transfer of Exogenous Nucleic Acid Sequences to other Bacterial Species Using the E. coli Expression

Vectors or Expression Vectors Functional in Bacterial Species other than E. coli.

Molecule No. EcXA059, encoding a portion of the ypjA gene of Escherichia coli, was either transformed directly into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae or subcloned into an expression vector functional in these species and the subclones transformed into these organisms. Suitable expression vectors are well known in the art. These expression vectors were introduced into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae cells that were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. If there was no effect of antisense RNA expression in one organism, the clone is given a score of zero "0" in that organism. In contrast, a score of "8" means that 10<sup>8</sup> times more cells were required to observe a colony formed on the induced state than in the non-induced state under the conditions used and in that organism.

Expression vectors containing Molecule No. EcXA059 were found to inhibit bacterial growth in all four organisms when expression of the antisense RNA was induced with IPTG. A score of 8 was assigned for *Escherichia coli*, *Enterobacter cloacae*, and *Salmonella typhimurium* and in *Klebsiella pneumoniae* the score was >7. The protein encoded by this sequence is used as a target sequence to screen candidate compound libraries as described above.

In addition, the above methods were validated using other antisense nucleic acids which inhibit the growth of *E. coli* which were identified using methods similar to those described above. Expression vectors which inhibited growth of *E. coli* upon induction of antisense RNA expression with IPTG were transformed directly into *Enterobacter cloacae*, *Klebsiella pneumonia* or *Salmonella typhimurium*. The transformed cells were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. The results of these experiments are listed in Table V below. If there was no effect of antisense RNA expression in a microorganism, the clone is minus in Table V below. In

contrast, a positive in Table V below means that at least 10 fold more cells were required to observe a colony on the induced plate than on the non-induced plate under the conditions used and in that microorganism.

Sixteen of the constructs were found to inhibit growth in all the microorganisms tested upon induction of antisense RNA expression with IPTG.

TABLE V

Sensitivity of Other Microorganisms to Antisense Nucleic Acids That Inhibit Proliferation in E. coli

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA001	+	+	<u> </u>
EcXA004	+	-	<u> </u>
EcXA005	+	+	+
EcXA006	•	-	-
EcXA007	•	+	-
EcXA008	+	•	+
EcXA009	-	- -	
EcXA010	+	+	+
EcXA011	-	+	-
EcXA012	-	+	-
EcXA013	+	+	+
EcXA014	+	+	-
EcXA015	+	+	+
EcXA016	+	+	+
EcXA017	+	+	+
EcXA018	+	+	+
EcXA019	+	+	+
EcXA020	+	+	+
EcXA021	+	+	+
EcXA023	+	+	+
EcXA024	+	-	+
EcXA025	-	•	-
EcXA026	+	+	-
EcXA027	+	+	-
EcXA028	+	-	-
EcXA029	-	-	•
EcXA030	+	+	+
EcXA031	+	-	-
EcXA032	+	+	-
EcXA033	+	+	+
EcXA034	+	+	+
EcXA035	-	-	-
EcXA036	+	-	+
EcXA037	+	+	<del>-</del>
EcXA038	+	+	+
EcXA039	+	<u> </u>	-
EcXA041	+	+	+
EcXA042	-	+	+

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Mol. No.	S. typhimurlum	E. cloacae	K. pneumoniae
EcXA043	-	-	-
EcXA044	-	•	•
EcXA045	+	+	+
EcXA046	•	-	
EcXA047	+	+	-
EcXA048	•	•	-
EcXA049	+	-	-
EcXA050		•	-
EcXA051	+	•	-
EcXA052	+	-	-
EcXA053	+	+	+
EcXA054	-	-	+
EcXA055	+	-	-
EcXA056	+	-	+
EcXA057	+	+	
EcXA058		-	-
EcXA059	+	+	+
EcXA060	-		<u>.</u>
EcXA061	<del>-</del> -	<u> </u>	
EcXA062	-	.=	-
EcXA063	+	+	
EcXA064	•		-
EcXA065	+	+	
EcXA066		-	_
EcXA067	-	+	-
EcXA068	1	-	
EcXA069	_	+	-
EcXA070	-	•	
EcXA071	+	-	-
EcXA072	+	•	+
EcXA073	+	+	+
EcXA074	+	+	+
EcXA075	+	•	-
EcXA076		+	-
EcXA077	+	+	_
EcXA079	+	+	+
EcXA080	+	<u>.                                    </u>	-
EcXA082	-	+	-
EcXA083	_		_
EcXA084	•	+	•
EcXA086	- · · · · · · · · · · · · · · · · · · ·	•	
EcXA087	-	• · · · · · · · · · · · · · · · · · · ·	-
EcXA088	_	-	•
EcXA089	<u> </u>	-	
EcXA090	-		
EcXA090	_	<u> </u>	•
EcXA091  EcXA092	<del> </del>		
EcXA092	-		
ECAAU93	<u> </u>		<u> </u>

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA094	+	+	+
EcXA095	+	+	-
EcXA096	-	-	-
EcXA097	+	-	
EcXA098	+	-	•
EcXA099	-	-	-
EcXA100		-	-
EcXA101	-	•	-
EcXA102	-	-	-
EcXA103		+	-
EcXA104	+	+	+
EcXA106	+	+	-
EcXA107	-	-	-
EcXA108	-	-	-
EcXA109	-	•	-
EcXA110	+	+	-
EcXA111	-	-	•
EcXA112	-	+	•
EcXA113	+	+	+
EcXA114	-	+	-
EcXA115	•	+	-
EcXA116	+	+	-
EcXA117	+	-	•
EcXA118	-	-	-
EcXA119	+	+	•
EcXA120	-	-	-
EcXA121	-	-	•
EcXA122	+		+
EcXA123	+	-	-
EcXA124	-	-	•
EcXA125		-	_
EcXA126	-	-	-
EcXA127	+	+	•
EcXA128	•	-	•
EcXA129	-	+	-
EcXA130	+	+	-
EcXA132	-	-	•
EcXA133	-	-	-
EcXA136	-	_	-
EcXA137	-	•	•
EcXA138	+	_	•
EcXA139	-	-	-
EcXA140	+	-	•
EcXA141	+	•	-
EcXA142	•	•	•
EcXA143	-	+	•
EcXA144	+	+	-
EcXA145	-		-

Mol No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA146		-	-
EcXA147	-	-	-
EcXA148	-	-	•
EcXA149	+	+	+
EcXA150	-	-	-
EcXA151	+	-	-
EcXA152	-	-	-
EcXA153	+	+	•
EcXA154	-	-	•
EcXA155	-	<u>-</u>	ND
EcXA156	-	+	-
EcXA157	-	-	-
EcXA158	-	-	-
EcXA159	+	-	-
EcXA160	+	_	-
EcXA162		-	-
EcXA163		-	•
EcXA164	-	-	-
EcXA165	-	-	<b>-</b>
EcXA166	•	-	
EcXA167	•	-	-
EcXA168	-	•	•
EcXA169	-	+	•
EcXA171	-	-	•
EcXA172	-	-	•
EcXA173	-	•	•
EcXA174	•	-	•
EcXA175	•	-	•
EcXA176	-	•	•
EcXA178	•	-	-
EcXA179	-	•	-
EcXA180	+	-	-
EcXA181	-	•	•
EcXA182	-	•	•
EcXA183	-	•	•
EcXA184	-	*	-
EcXA185	-	-	-
EcXA186	•	-	<b>-</b>
EcXA187	+	+	+
EcXA189	+	-	•
EcXA190	+	+	+
EcXA191	+	+	- · ·
EcXA192	-	+	•

Thus, the ability of an antisense nucleic acid which inhibits the proliferation of *E. coli* to inhibit the growth of other organims may be evaluated by either transforming the antisense nucleic acid directly into other *Escherichia* species or inserting the antisense nucleic acid into expression

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vectors that are functional in other Gram negative species such as *Enterobacter cloacae*, *Salmonella typhimurium*, and/or Klebsiella pneumoniae. Similarly, the antisense nucleic acid can be inserted in expression vectors that are functional in Gram-positive species such as *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* or other species.

Those skilled in the art will appreciate that a negative result in a heterologous microorganism does not mean that that microorganism is missing that gene nor does it mean that the gene is unessential. However, a positive result means that the heterologous microorganism contains a homologous gene which is required for proliferation of that microorganism. The homologous gene may be obtained using the methods described herein. Those cells that are inhibited by antisense may be used in cell based assays as described herein for the identification and characterization of compounds in order to develop antibiotics effective in these microorganisms. Those skilled in the art will appreciate that an antisense molecule which works in the microorganism from which it was obtained will not always work in a heterologous microorganism.

#### **EXAMPLE 13**

#### Use of Identified Exogenous Nucleic Acid Sequences as Probes

The identified sequence of the present invention can be used as probes to obtain the sequence of additional genes of interest from a second organism. For example, probes to potential bacterial target proteins may be hybridized to nucleic acids from other organisms including other bacteria and higher organisms, to identify homologous sequences. Such hybridization might indicate that the protein encoded by the gene to which the probe corresponds is found in humans and therefore not necessarily a good drug target. Alternatively, the gene can be conserved only in bacteria and therefore would be a good drug target for a broad spectrum antibiotic or antimicrobial.

Probes derived from the identified nucleic acid sequences of interest or portions thereof can be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe can be single stranded or double stranded and can be made using techniques known in the art, including *in vitro* transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it can be denatured prior to contacting the probe. In some applications, the nucleic acid sample can be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample can comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe can be cloned into vectors such as expression vectors, sequencing vectors, or in

vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques can be used to isolate, purify and clone sequences from a genomic library, made from a variety of bacterial species, which are capable of hybridizing to probes made from the sequences identified in Examples 5 and 6.

**EXAMPLE 14** 

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#### Preparation of PCR Primers and Amplification of DNA

The identified E. coli genes corresponding directly to or located within the operon of nucleic acid sequences required for proliferation or portions thereof can be used to prepare PCR primers for a variety of applications, including the identification or isolation of homologous sequences from other species, for example S. typhimurium, E. cloacae, and Klebsiella pneumoniae, which contain part or all of the homologous genes. Because homologous genes are related but not identical in sequence, those skilled in the art will often employ degenerate sequence PCR primers. Such degenerate sequence primers are designed based on conserved sequence regions, either known or suspected, such as conserved coding regions. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. The PCR primers are at least 10 bases, and preferably at least 20 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers can be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. When the entire coding sequence of the target gene is known, the 5' and 3' regions of the target gene can be used as the sequence source for PCR probe generation. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

#### **EXAMPLE 15**

### Inverse PCR

The technique of inverse polymerase chain reaction can be used to extend the known nucleic acid sequence identified in Examples 5 and 6. The inverse PCR reaction is described generally by Ochman et al., in Ch. 10 of PCR Technology: Principles and Applications for DNA Amplification, (Henry A. Erlich, Ed.) W.H. Freeman and Co. (1992). Traditional PCR requires two primers that are

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used to prime the synthesis of complementary strands of DNA. In inverse PCR, only a core sequence need he known.

Using the sequences identified as relevant from the techniques taught in Examples 5 and 6 and applied to other species of bacteria, a subset of exogenous nucleic sequences are identified that correspond to genes or operons that are required for bacterial proliferation. In species for which a genome sequence is not known, the technique of inverse PCR provides a method for obtaining the gene in order to determine the sequence or to place the probe sequences in full context to the target sequence to which the identified exogenous nucleic acid sequence binds.

To practice this technique, the genome of the target organism is digested with an appropriate restriction enzyme so as to create fragments of nucleic acid that contain the identified sequence as well as unknown sequences that flank the identified sequence. These fragments are then circularized and become the template for the PCR reaction. PCR primers are designed in accordance with the teachings of Example 15 and directed to the ends of the identified sequence are synthesized. The primers direct nucleic acid synthesis away from the known sequence and toward the unknown sequence contained within the circularized template. After the PCR reaction is complete, the resulting PCR products can be sequenced so as to extend the sequence of the identified gene past the core sequence of the identified exogenous nucleic acid sequence identified. In this manner, the full sequence of each novel gene can be identified. Additionally the sequences of adjacent coding and noncoding regions can be identified.

## **EXAMPLE 16**

Identification of Genes Required for Staphylococcus aureus Proliferation

Genes required for proliferation in *Staphylococcus aureus* are identified according to the methods described above.

#### **EXAMPLE 17**

## Identification of Genes Required for Neisseria gonorrhoeae Proliferation

Genes required for proliferation in *Neisseria gonorrhoeae* are identified according to the methods described above.

## **EXAMPLE 18**

### Identification of Genes Required for Pseudomonas aeruginosa Proliferation

Genes required for proliferation in *Pseudomonas aeruginosa* are identified according to the methods described above.

## **EXAMPLE 19**

# Identification of Genes Required for Enterococcus faecalis Proliferation

Genes required for proliferation in *Enterococcus faecalis* are identified according to the methods described above.

### **EXAMPLE 20**

# Identification of Genes Required for Haemophilus influenzae Proliferation

Genes required for proliferation in *Haemophilus influenzae* are identified according to the methods described above.

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#### **EXAMPLE 21**

#### Identification of Genes Required for Salmonella typhimurium Proliferation

Genes required for proliferation in Salmonella typhimurium are identified according to the methods described above.

### **EXAMPLE 22**

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# Identification of Genes Required for Helicobacter pylori Proliferation

Genes required for proliferation in *Helicobacter pylori* are identified according to the methods described above.

#### EXAMPLE 23

# Identification of Genes Required for Mycoplasma pneumoniae Proliferation

Genes required for proliferation in *Mycoplasma pneumoniae* are identified according to the methods described above.

### **EXAMPLE 24**

## Identification of Genes Required for Plasmodium ovale Proliferation

Genes required for proliferation in *Plasmodium ovale* are identified according to the methods described above.

#### **EXAMPLE 25**

## Identification of Genes Required for Saccharomyces cerevisiae Proliferation

Genes required for proliferation in Saccharomyces cerevisiae are identified according to the methods described above.

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# **EXAMPLE 26**

# Identification of Genes Required for Entamoeba histolytica Proliferation

Genes required for proliferation in *Entamoeba histolytica* are identified according to the methods described above.

## **EXAMPLE 27**

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# Identification of Genes Required for Candida albicans Proliferation

Genes required for proliferation in *Candida albicans* are identified according to the methods described above.

#### **EXAMPLE 28**

# Identification of Genes Required for Klebsiella pneumoniae Proliferation

Genes required for proliferation in *Klebsiella pneumoniae* are identified according to the methods described above.

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# Identification of Genes Required for Salmonella typhi Proliferation

Genes required for proliferation in Salmonella typhi are identified according to the methods described above.

#### **EXAMPLE 30**

10 Identification of Genes Required for Salmonella paratyphi Proliferation

Genes required for proliferation in Salmonella paratyphi are identified according to the methods described above.

### **EXAMPLE 31**

# Identification of Genes Required for Salmonella cholerasuis Proliferation

Genes required for proliferation in Salmonella cholerasuis are identified according to the methods described above.

#### **EXAMPLE 32**

# Identification of Genes Required for Staphylococcus epidermis Proliferation

Genes required for proliferation in *Staphylococcus epidermis* are identified according to the methods described above.

#### **EXAMPLE 33**

## Identification of Genes Required for Mycobacterium tuberculosis Proliferation

Genes required for proliferation in *Mycobacterium tuberculosis* are identified according to the methods described above.

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### Identification of Genes Required for Mycobacterium leprae Proliferation

Genes required for proliferation in *Mycobacterium leprae* are identified according to the methods described above.

# **EXAMPLE 35**

30 <u>Identification of Genes Required for Treponema pallidum Proliferation</u>

Genes required for proliferation in *Treponema pallidum* are identified according to the methods described above.

# **EXAMPLE 36**

## Identification of Genes Required for Bacillus anthracis Proliferation

35 Genes required for proliferation in *Bacillus anthracis* are identified according to the methods described above.

## **EXAMPLE 37**

## Identification of Genes Required for Yersinia pestis Proliferation

Genes required for proliferation in Yersinia pestis are identified according to the methods described above.

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#### **EXAMPLE 38**

## Identification of Genes Required for Clostridium botulinum Proliferation

Genes required for proliferation in *Clostridium botulinum* are identified according to the methods described above.

#### **EXAMPLE 39**

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## Identification of Genes Required for Campylobacter jejuni Proliferation

Genes required for proliferation in *Campylobacter jejuni* are identified according to the methods described above.

### **EXAMPLE 40**

# Identification of Genes Required for Chlamydia trachomatis Proliferation

Genes required for proliferation in *Chlamydia trachomatis* are identified according to the methods described above.

## Use of Isolated Exogenous Nucleic Acid Fragments as Antisense Antibiotics

In addition to using the identified sequences to enable screening of molecule libraries to identify compounds useful to identify antibiotics, the sequences themselves can be used as therapeutic agents. Specifically, the identified exogenous sequences in an antisense orientation can be provided to an individual to inhibit the translation of a bacterial target gene.

#### Generation of Antisense Therapeutics from Identified Exogenous Sequences

The sequences of the present invention can be used as antisense therapeutics for the treatment of bacterial infections or simply for inhibition of bacterial growth in vitro or in vivo. The therapy exploits the biological process in cells where genes are transcribed into messenger RNA (mRNA) that is then translated into proteins. Antisense RNA technology contemplates the use of antisense oligonucleotides directed against a target gene that will bind to its target and decrease or inhibit the translation of the target mRNA. In one embodiment, antisense oligonucleotides can be used to treat and control a bacterial infection of a cell culture containing a population of desired cells contaminated with bacteria. In another embodiment, the antisense oligonucleotides can be used to treat an organism with a bacterial infection.

Antisense oligonucleotides can be synthesized from any of the sequences of the present invention using methods well known in the art. In a preferred embodiment, antisense oligonucleotides are synthesized using artificial means. Uhlmann & Peymann, Chemical Rev. 90:543-584 (1990) review antisense oligonucleotide technology in detail. Modified or unmodified

antisense oligonucleotides can be used as therapeutic agents. Modified antisense oligonucleotides are preferred since it is well known that antisense oligonucleotides are extremely unstable. Modification of the phosphate backbones of the antisense oligonucleotides can be achieved by substituting the internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate bridges, thioester bridges, as well as many others known in the art. The preparation of certain antisense oligonucleotides with modified internucleotide linkages is described in U.S. Patent No. 5,142,047.

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Modifications to the nucleoside units of the antisense oligonucleotides are also contemplated. These modifications can increase the half-life and increase cellular rates of uptake for the oligonucleotides in vivo. For example,  $\alpha$ -anomeric nucleotide units and modified bases such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1-phenylribofuranose, and  $N^4$ ,  $N^4$ -ethano-5-methylcytosine are contemplated for use in the present invention.

An additional form of modified antisense molecules is found in peptide nucleic acids. Peptide nucleic acids (PNA) have been developed to hybridize to single and double stranded nucleic acids. PNA are nucleic acid analogs in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units. Unlike DNA, which is highly negatively charged, the PNA backbone is neutral. Therefore, there is much less repulsive energy between complementary strands in a PNA-DNA hybrid than in the comparable DNA-DNA hybrid, and consequently they are much more stable. PNA can hybridize to DNA in either a Watson/Crick or Hoogsteen fashion (Demidov et al., *Proc. Natl. Acad. Sci. U.S.A.* 92:2637-2641, 1995; Egholm, *Nature* 365:566-568, 1993; Nielsen et al., *Science* 254:1497-1500, 1991; Dueholm et al., *New J. Chem.* 21:19-31, 1997).

Molecules called PNA "clamps" have been synthesized which have two identical PNA sequences joined by a flexible hairpin linker containing three 8-amino-3,6-dioxaoctanoic acid units. When a PNA clamp is mixed with a complementary homopurine or homopyrimidine DNA target sequence, a PNA-DNA-PNA triplex hybrid can form which has been shown to be extremely stable (Bentin et al., *Biochemistry* 35:8863-8869, 1996; Egholm et al., *Nucleic Acids Res.* 23:217-222, 1995; Griffith et al., *J. Am. Chem. Soc.* 117:831-832, 1995).

The sequence-specific and high affinity duplex and triplex binding of PNA have been extensively described (Nielsen et al., Science 254:1497-1500, 1991; Egholm et al., J. Am. Chem. Soc. 114:9677-9678, 1992; Egholm et al., Nature 365:566-568, 1993; Almarsson et al., Proc. Natl. Acad. Sci. U.S.A. 90:9542-9546, 1993; Demidov et al., Proc. Natl. Acad. Sci. U.S.A. 92:2637-2641, 1995). They have also been shown to be resistant to nuclease and protease digestion (Demidov et al., Biochem. Pharm. 48:1010-1313, 1994). PNA has been used to inhibit gene expression (Hanvey et al., Science 258:1481-1485,1992; Nielsen et al., Nucl. Acids. Res., 21:197-200, 1993; Nielsen et al., Gene

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149:139-145, 1994; Good & Nielsen, Science, 95: 2073-2076, 1998), to block restriction enzyme activity (Nielsen et al., supra, 1993), to act as an artificial transcription promoter (Mollegaard, Proc. Natl. Acad. Sci. U.S.A. 91:3892-3895, 1994) and as a pseudo restriction endonuclease (Demidov et al., Nucl. Acids. Res. 21:2103-2107, 1993). Recently, PNA has also been shown to have antiviral and antitumoral activity mediated through an antisense mechanism (Norton, Nature Biotechnol., 14:615-619, 1996; Hirschman et al., J. Investig. Med. 44:347-351, 1996). PNAs have been linked to various peptides in order to promote PNA entry into cells (Basu et al., Bioconj. Chem. 8:481-488, 1997; Pardridge et al., Proc. Natl. Acad. Sci. U.S.A. 92:5592-5596, 1995).

The antisense oligonucleotides contemplated by the present invention can be administered by direct application of oligonucleotides to a target using standard techniques well known in the art. The antisense oligonucleotides can be generated within the target using a plasmid, or a phage. Alternatively, the antisense nucleic acid may be expressed from a sequence in the chromosome of the target cell. It is further contemplated that contemplated that the antisense oligonucleotide contemplated are incorporated in a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991). The present invention also contemplates using a retron to introduce an antisense oligonucleotide to a cell. Retron technology is exemplified by U.S. Patent No. 5,405,775. Antisense oligonucleotides can also be delivered using liposomes or by electroporation techniques which are well known in the art.

The antisense nucleic acids of the present invention can also be used to design antibiotic compounds comprising nucleic acids which function by intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. The sequences identified as required for proliferation in the present invention, or portions thereof, can be used as templates to inhibit microorganism gene expression in individuals infected with such organisms. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences based on the sequences of the present invention that are required for proliferation are contemplated for use as antibiotic compound templates.

The antisense oligonucleotides of this example employ the identified sequences of the present invention to induce bacterial cell death or at least bacterial stasis by inhibiting target gene translation. Antisense oligonucleotides containing from about 8 to 40 bases of the sequences of the present invention have sufficient complementary to form a duplex with the target sequence under physiological conditions.

To kill bacterial cells or inhibit their growth, the antisense oligonucleotides are applied to the bacteria or to the target cells under conditions that facilitate their uptake. These conditions

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include sufficient incubation times of cells and oligonucleotides so that the antisense oligonucleotides are taken up by the cells. In one embodiment, an incubation period of 7-10 days is sufficient to kill bacteria in a sample. An optimum concentration of antisense oligonucleotides is selected for use.

The concentration of antisense oligonucleotides to be used can vary depending on the type of bacteria sought to be controlled, the nature of the antisense oligonucleotide to be used, and the relative toxicity of the antisense oligonucleotide to the desired cells in the treated culture. Antisense oligonucleotides can be introduced to cell samples at a number of different concentrations preferably between  $1 \times 10^{-10} M$  to  $1 \times 10^{-4} M$ . Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of  $1 \times 10^{-7}$  translates into a dose of approximately 0.6 mg/kg body weight. Levels of oligonucleotide approaching 100 mg/kg body weight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the subject are removed, treated with the antisense oligonucleotide, and reintroduced into the subject. This range is merely illustrative and one of skill in the art are able to determine the optimal concentration to be used in a given case.

After the bacterial cells have been killed or controlled in a desired culture, the desired cell population may be used for other purposes.

#### **EXAMPLE 41**

The following example demonstrates the ability of an *E. coli* antisense oligonucleotide to act as a bactericidal or bacteriostatic agent to treat a contaminated cell culture system. The application of the antisense oligonucleotides of the present invention are thought to inhibit the translation of bacterial gene products required for proliferation.

The antisense oligonucleotide of this example corresponds to a 30 base phophorothioate modified oligodeoxynucelotide complementary to a nucleic acid involved in proliferation, such as Molecule Number EcXA056 (SEQ ID NO: 1). A sense oligodeoxynucelotide complementary to the antisense sequence is synthesized and used as a control. The oligonucleotides are synthesized and purified according to the procedures of Matsukura, et al., Gene 72:343 (1988). The test oligonucleotides are dissolved in a small volume of autoclaved water and added to culture medium to make a 100 micromolar stock solution.

Human bone marrow cells are obtained from the peripheral blood of two patients and cultured according standard procedures well known in the art. The culture is contaminated with the K-12 strain of *E. coli* and incubated at 37°C overnight to establish bacterial infection.

The control and antisense oligonucleotide containing solutions are added to the contaminated cultures and monitored for bacterial growth. After a 10 hour incubation of culture and oligonucleotides, samples from the control and experimental cultures are drawn and analyzed

for the translation of the target bacterial gene using standard microbiological techniques well known in the art. The target *E. coli* gene is found to be translated in the control culture treated with the control oligonucleotide, however, translation of the target gene in the experimental culture treated with the antisense oligonucleotide of the present invention is not detected or reduced.

**EXAMPLE 42** 

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A subject suffering from an *E. coli* infection is treated with the antisense oligonucleotide preparation of Example 39. The antisense oligonucleotide is provided in a pharmaceutically acceptable carrier at a concentration effective to inhibit the translation of the target gene. The present subject is treated with a concentration of antisense oligonucleotide sufficient to achieve a blood concentration of about 100 micromolar. The patient receives daily injections of antisense oligonucleotide to maintain this concentration for a period of 1 week. At the end of the week a blood sample is drawn and analyzed for the presence or absence using standard techniques well known in the art. There is no detectable evidence of E. coli and the treatment is terminated.

### **EXAMPLE 43**

## Preparation and use of Triple Helix Probes

The sequences of microorganism genes required for proliferation of the present invention are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches that could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into a population of bacterial cells that normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides can be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for a reduction in proliferation using techniques such as monitoring growth levels as compared to untreated cells using optical density measurements. The oligonucleotides that are effective in inhibiting gene expression in cultured cells can then be introduced in vivo using the techniques well known in that art at a dosage level shown to be effective.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-971 (1989)).

#### **EXAMPLE 44**

## Identification of Bacterial Strains from Isolated Specimens by PCR

Classical bacteriological methods for the detection of various bacterial species are time consuming and costly. These methods include growing the bacteria isolated from a subject in specialized media, cultivation on selective agar media, followed by a set of confirmation assays that can take from 8 to 10 days or longer to complete. Use of the identified sequences of the present invention provides a method to dramatically reduce the time necessary to detect and identify specific bacterial species present in a sample.

In one exemplary method, bacteria are grown in enriched media and DNA samples are isolated from specimens of, for example, blood, urine, stool, saliva or central nervous system fluid by conventional methods. A panel of PCR primers based on identified sequences unique to various species of microorganisms are then utilized in accordance with Example 12 to amplify DNA of approximately 100-200 bases in length from the specimen. A separate PCR reaction is set up for each pair of PCR primers and after the PCR reaction is complete, the reaction mixtures are assayed for the presence of PCR product. The presence or absence of bacteria from the species to which the PCR primer pairs belong is determined by the presence or absence of a PCR product in the various test PCR reaction tubes.

Although the PCR reaction is used to assay the isolated sample for the presence of various bacterial species, other assays such as the Southern blot hybridization are also contemplated.

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## WHAT IS CLAIMED IS:

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1. A purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 1-127, wherein expression of said nucleic acid inhibits proliferation of a microorganism.

- 2. The nucleic acid sequence of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a microorganism.
- 3. The nucleic acid of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of an RNA required for proliferation of a microorganism.
- 4. The nucleic acid of Claim 3, wherein said RNA is an RNA encoding more than one gene product.
- 5. A nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-127, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive bases of one of SEQ ID NOs: 1-127.
- 6. A vector comprising a promoter operably linked to the nucleic acid sequence of Claims 1,2,3,4, or 5.
- 7. The vector of Claim 6, wherein said promoter is active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
  - 8. A host cell containing the vector of Claim 6 or Claim 7.
- A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 128-298.
- 10. A fragment of the nucleic acid of Claim 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 128-298.
  - 11. A vector comprising a promoter operably linked to the nucleic acid of Claim 9 or Claim 10.
- 12. A purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region

within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.

- 13. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-127, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127, the sequences complementary to SEQ ID NOs.: 1-127 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127 as determined using BLASTN version 2.0 with the default parameters.
- 14. The nucleic acid of Claim 13, wherein said nucleic acid is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Staphylococcus aureus, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
- 15. A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.
  - 16. A host cell containing the vector of Claim 16.

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- 17. The vector of Claim 15, wherein said polypeptide comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-469.
- 18. A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.
- 19. The polypeptide of Claim 18, wherein said polypeptide comprises a polypeptide comprising one of SEQ ID NOs.: 299-469 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 20. A purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or at least 25% identity to a fragment comprising at least 5, at

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least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127 as determined using FASTA version 3.0t78 with the default parameters.

- 21. The polypeptide of Claim 20, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-469 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-469 as determined using FASTA version 3.0t78 with the default parameters.
- 22. An antibody capable of specifically binding the polypeptide of one of Claims 18-21.
- 23. A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 into a cell.
  - 24. The method of Claim 23, further comprising the step of isolating said polypeptide.
- 25. The method of Claim 23, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 26. A method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.
- 27. The method of Claim 26, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 28. A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

contacting said gene product with a candidate compound; and determining whether said compound influences the activity of said gene product.

- 29. The method of Claim 28, wherein said gene product is a polypeptide and said activity is an enzymatic activity.
- 30. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.
- 31. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.

32. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transporter activity.

- 33. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transcriptional activity.
- 34. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a DNA replication activity.
- 35. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a cell division activity.
  - 36. A compound identified using the method of Claim 28.

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- 10 37. The method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
  - 38. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:
    - (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
      - (b) contacting said target with a candidate compound or nucleic acid; and
      - (c) measuring an activity of said target.
  - 39. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.
    - 40. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.
- 41. The method of Claim 38, wherein said target is a gene and said activity is transcription of said gene.
  - 42. The method of Claim 38, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.
- 43. The method of Claim 38, wherein said target gene or RNA encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
  - 44. A compound or nucleic acid identified using the method of Claim 38.
  - 45. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising the steps of:

(a) expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

(b) contacting said sensitized cell with a compound; and

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- (c) determining whether said compound inhibits the growth of said sensitized cell.
- 46. The method of Claim 45, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
- 47. The method of Claim 45, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
  - 48. The method of Claim 45, wherein said cell is a Gram negative bacterium.
  - 49. The method of Claim 45, wherein said cell is an E. coli cell.
- 50. The method of Claim 45, wherein said cell is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
  - 51. The method of Claim 45, wherein said antisense nucleic acid is transcribed from an inducible promoter.
- 52. The method of Claim 51, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level.
- 53. The method of Claim 45, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.
  - 54. The method of Claim 45, wherein said gene product is a polypeptide.
- 55. The method of Claim 54, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
  - 56. The method of Claim 45, wherein said gene product is an RNA.
  - 57. A compound identified using the method of Claim 45.
- 58. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid

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comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a compound with activity against the product of said gene into a population of cells expressing said gene.

- 59. The method of Claim 58, wherein said compound is an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof.
- 60. The method of Claim 59, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-127 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive bases of one of SEQ ID NOs.: 1-127.
- 61. The method of Claim 58, wherein said population is a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
- 62. The method of Claim 58, wherein said population is a population of Gram negative bacteria.
  - 63. The method of Claim 58, wherein said population is a population of *E. coli* cells.
- 64. The method of Claim 58, wherein said population is a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa,Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis cells or cells from any species falling within the genera of any of the above species.
  - 65. The method of Claim 58, wherein said gene encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
  - 66. A preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.
  - 67. The preparation of Claim 66, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-127 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.
  - 68. A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon.

69. The method of Claim 68, wherein said antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a proliferation inhibiting portion thereof.

70. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

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- 71. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population.
- 72. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.
- 73. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.
- 74. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.
- 75. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.
- 76. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.
- 77. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid.
- 78. The method of Claim 68, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.
  - 79. The method of Claim 68 wherein said antisense nucleic acid is an oligonucleotide.
- 80. A method for identifying a gene which is required for proliferation of a microorganism comprising:
  - (a) contacting a microorganism other than *E. coli* with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127;
  - (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
  - (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.
- 81. The method of Claim 80, wherein said microorganism is a Gram negative 35 bacterium.

82. The method of Claim 80 wherein said microorganism is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

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- 83. The method of Claim 80, further comprising introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.
- 84. A method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:
  - (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127;
  - (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
  - (c) contacting said first microorganism with a sublethal level of said inhibitory
     nucleic acid, thus sensitizing said first microorganism;
    - (d) contacting the sensitized microorganism of step (c) with a compound; and
  - (e) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 85. The method of Claim 84, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
- 86. The method of Claim 84 wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

87. The method of Claim 84 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene.

88. The method of Claim 84 wherein the step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 in said microorganism.

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- 89. The method of Claim 84, wherein said inhibitory nucleic acid is an antisense nucleic acid.
- 90. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.
- 91. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.
  - 92. The method of Claim 84, wherein the step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid comprises directly contacting said microorganism with said inhibitory nucleic acid.
  - 93. The method of Claim 84, wherein the step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said microorganism.
  - 94. The method of Claim 84, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
    - 95. A compound identified using the method of Claim 84.
  - 96. A method of identifying a compound having the ability to inhibit proliferation comprising:
    - (a) contacting a microorganism other than *E. coli* with a sublethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
      - (b) contacting the sensitized microorganism of step (a) with a compound; and
    - (c) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 30 97. The method of Claim 96, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
  - 98. A compound identified using the method of Claim 96.
- 99. A method for identifying a compound having activity against a biological pathway35 required for proliferation comprising:

(a) sensitizing a cell by expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, in said cell to reduce the activity or amount of said gene product;

(b) contacting the sensitized cell with a compound; and

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- (c) determining whether said compound inhibits the growth of said sensitized cell.
- 100. The method of Claim 99, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
  - 101. The method of Claim 99, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
    - 102. The method of Claim 99, wherein said cell is a Gram negative bacterium.
    - 103. The method of Claim 99, wherein said Gram negative bacterium is E. coli.
  - 104. The method of Claim 99, wherein said cell is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
  - 105. The method of Claim 99, wherein said antisense nucleic acid is transcribed from an inducible promoter.
  - 106. The method of Claim 99, further comprising contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level.
  - 107. The method of Claim 99, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.
  - 108. The method of Claim 99, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
    - 109. A compound identified using the method of Claim 99.
- 110. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

(a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127;

(b) contacting said cell with a compound; and

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- (c) determining whether said compound reduces proliferation of said contacted cell.
- 111. The method of Claim 110, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.
- 112. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.
- 113. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a microorganism.
- 114. The method of Claim 110, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.
- 115. The method of Claim 114, wherein said mutation is a temperature sensitive mutation.
  - 116. The method of Claim 110, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
    - 117. A compound identified using the method of Claim 110.
- 25 gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:
  - (a) expressing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;
  - (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
    - (c) determining whether said cell is sensitive to said compound.
- 119. The method of Claim 118, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid and wherein said gene or gene product

lies in the same pathway on which said compound acts if said cell expressing said sublethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sublethal level of said antisense nucleic acid.

- 120. The method of Claim 118, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
  - 121. A method for determining the biological pathway on which a test compound acts comprising:
    - (a) expressing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
      - (b) contacting said cell with said test compound; and
      - (c) determining whether said cell is sensitive to said test compound.
- 122. The method of Claim 121, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.
  - 123. The method of Claim 121, further comprising:

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- (d) expressing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and
- (e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.
- 124. A purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127.
  - 125. A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.
- 126. A compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.
  - 127. A method for manufacturing an antibiotic comprising the steps of:

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screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127; and manufacturing the compound so identified.

- 128. The method of Claim 127, wherein said screening step comprises performing any one of the methods of Claims 28, 38, 45, 96, 99 and 110.
- 129. A method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 to said subject.
- 130. The method of Claim 129 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.
- 131. The method of Claim 129, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

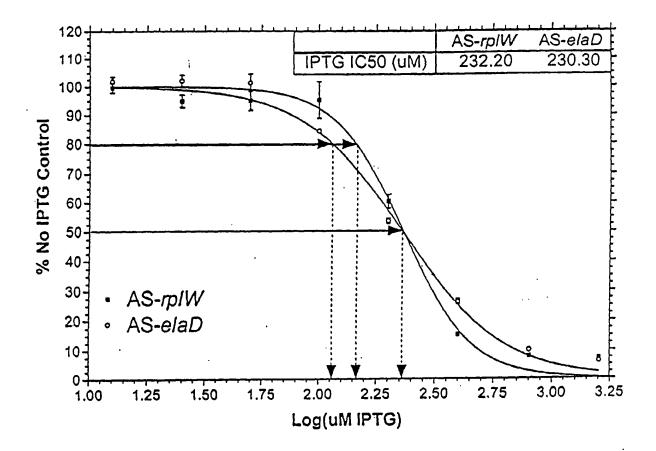


Figure . \

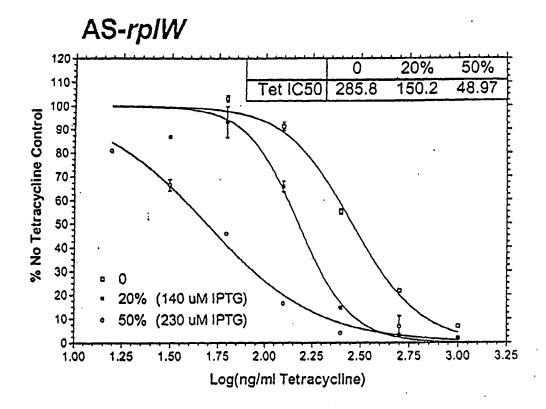


Figure & A

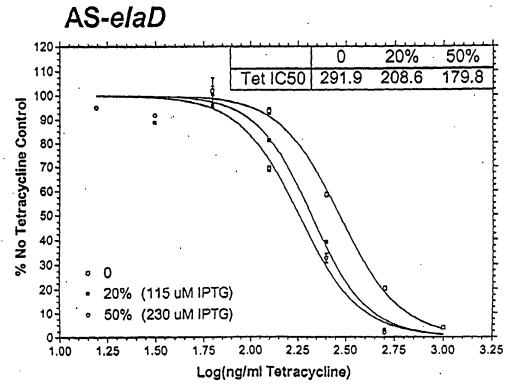


Figure aB

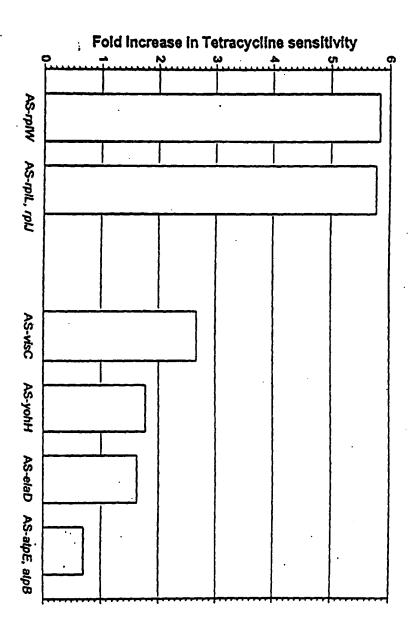


Figure 3

### SEQUENCE LISTING

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gacgettacg ttgacgacgg teacggtaag catactgace agetttgata acageetgga
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tcttgtgacg tgcacgtgca ataacaccac gttttacgcg agccatatgt gctctcctgt
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atctatattc taattaaaaa qttaaaaacg ttaacggctt atgcgtacgg caggcacgcg
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attaccaqqc ccaqatcgcc tttggaaacc atggctttcg gacgcaggtg acgtttacgt
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ttaccggttt ttttgaagcg cttagcagca ccgcgtacgg tcttaatttt tggcatttta
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actaaacagg ggaaaacaat tacagatttt tatctttcga ttacgatttt tggtttattt
                                                                       180
                                                                       222
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<211> 278
<212> DNA
<213> Escherichia coli
<400> 25
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                                                                       120
                                                                       180
atggatgtag ttatcaaatt gaatttaaag tgaaaatatt tttacgggcg ggggcaagaa
ggacatataa acaaatacgc cctcggaaaa tccagagggc gtcgggcaat taaaccggtg
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taattccatt gctatctcct tacgccttca cagctggttt aacgatcagg tcgctaccgg
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gctaccggtt gcacccggga cagcaccttt aaccagcagc aggttgcgct cagcgtcaac
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gcgtactacg tcaaggctct gaacggttac acgttcgtta cccatctgac ctgccatttt
                                                                       240
                                                                       266
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cgccttcaca gctggtttaa cgatcaggtc gctaccggtt gcacccggga cagcaccttt
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acggttaget tttttageac cggtggtcac ctgaatagea cggtageeat cgttageeag
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                                                                       180
cqctcaacqt caacqcqtac tacqtcaaqq ctctgaacqg gtacacqttc gttacccatn
                                                                       225
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ctacqcqqcq caqctctttc gctttaggca gagtcgtctt gatgatttca tgacgaacca
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                                                                       300
acqacqatta qcaacqctat cagtcttgqc aagagtaatc agcggctcaa ctacqcggcg
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tattatatcq tatqtataat catqtaaaat accattcqtt gttattqqca taaatqcqaa
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agcaaccatc aattqtqcat tqtttqattt aaattttatt tqaqaqtcag taacacttga
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                                                                       120
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gcttcagcag acagttccgg cagcaggctg ctggagcttt ttgccttcta tcaaagcctg
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                                                                       360
ctaactgcct tacaggggca gaccgatccg ctggaaatta ttgccgatcg ctttaaagcc
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cqaaactgac gtgctctgtt ttgacgaatt ttttgtttct gatattaccc gatgccatgc
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tacttggcgg tctgatgaaa gccctgttcg ctcgcggtat taccctggta gcgacgtcaa
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agacgagcgc ggcctttagc acgacgacgt gccagaacct gacgaccatt tttagtagcc
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conntnncan agnactnega ntnncennen tnnngenttt nngnngennt atnnangetg
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connanneth enneegenen nnnnetenat ntnttnnngn tetennntgn ennnnnnntn
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agtgatecaa etggetgeca eegtttgeeg cacaggtatt aaataaetee tggeaggteg
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attaattcca gcgcctgcac taacgcagag tgatccaact ggctgccacc gtttgccgca
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caggta
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attaattcca qcgcctgcac taacgcagag tgatccaact ggctgccacc gtttgccgca
                                                                  240
                                                                  300
caggtattaa ataactcctg gcaggtcgca gtgtttggca ggttcagcgc aagtgctttc
qcactttgca gtgccaggtt gagatctttc tggtgcagag cgattttgaa gcccggatta
                                                                  360
                                                                  420
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cccatcagcg cctggcgcac acgtaccggg tccgcaccgg cttttgaagc aaatagcagg
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tagtcgcggg acgcatacaa acataacccc tggatgttat gtgtctatcg agaatcaaag
                                                                       180
                                                                       240
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tgtatctatc actgttgatg ataatatcag cacttggttc tggagggggt ttgttgtggg
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                                                                       360
agggcatttg atagtcaata ccgcaattct atcaggagat atagtcactc taagaggagg
                                                                       420
agaaattagg ttggtattat agcttgtgcg cgccatgatt ggcgcgcaat ttaaacttag
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ttattcaggt ctacattatt ctctattttg gtcagtttta tgagttcatt tacagccata
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                                                                       180
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gtg Val	gaa Glu 50	aat Asn	gac Asp	ggt Gly	ggt Gly	tct Ser 55	ctg Leu	gaa Glu	gcc Ala	atc Ile	gcc Ala 60	aaa Lys	aaa Lys	tac Tyr	aac Asn	192
gtc Val 65	ggc Gly	ttt Phe	ctc Leu	gct Ala	ctg Leu 70	tta Leu	cag Gln	gct Ala	aac Asn	ccc Pro 75	ggc Gly	gtt Val	gat Asp	cct Pro	tac Tyr 80	240
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cca Pro	gat Asp	gcg Ala	ccg Pro 100	cgc Arg	gaa Glu	ggc Gly	att Ile	gtg Val 105	atc Ile	aac Asn	att Ile	gcg Ala	gag Glu 110	ctg Leu	cgt Arg	336
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acc Thr 145	Val	tca Ser	gac Asp	aaa Lys	cgt Arg 150	gca Ala	aac Asn	cca Pro	acc Thr	tgg Trp 155	Thr	cca Pro	acg Thr	gca Ala	aac Asn 160	480
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aac Asr	gat Asp	aaa Lys 275	Ile	aga Arg	att Ile	atg Met	agc Ser 280	Glu	ago Ser	aaa Lys	gag Glu	aat Asn 285	тте	aaa Lys	cac His	864		
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tca Sea 305	Asr	gat Asp	cat His	gtt Val	att . Ile 310	Asr	caa Glr	tct Ser	gtt Val	gca L Ala 315	i Ile	a att	cca Pro	gca Ala	ctt Leu 320	960		•
cc; Pro	g aaa o Lys	ı gaa Glu	a caq ı Glı	g cta n Leu 329	ı Leı	g ato 1 Met	g tta Leu	a aaa 1 Lys	a gga s Gly 330	y Sei	t gto	g gat L Asp	gaa Glu	ata 1116 335	a acc Thr	1008	٠	
cc <sup>1</sup>	t cca	tta Lev	a toa u Se:	a cci	gca Ala	a acq	g ato r Met	aat Asi	tte	g cta u Le	a ato u Me	g gca t Ala	a att	ggt Gl	cag y Gln	1056		

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atc ctt aat aca tta Ile Leu Asn Thr Leu 690	aat aag atg Asn Lys Met 695	g gct gaa agc : Ala Glu Ser	ttt ggc ttt a Phe Gly Phe T 700	acg gat 2112 Thr Asp
aac cct cga tac att Asn Pro Arg Tyr Ile 705	gcg gag aaa Ala Glu Lys 710	a aat tat atg s Asn Tyr Met 715	Glu Ala Leu I	etc aaa 2160 Leu Lys 720
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atc tac ggt aaa tto Ile Tyr Gly Lys Phe 35	atc aag cg Ile Lys Ar 4	g Thr Thr Lys	a ctg cac gta s Leu His Val 45	cat gac 144 His Asp

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cgt Arg 65	ccg Pro	ctg Leu	tcc Ser	aag Lys	act Thr 70	aaa Lys	tcc Ser	tgg Trp	acg Thr	ctg Leu 75	gtt Val	cgc Arg	gtt Val	gta Val	gag Glu 80	240
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WO 01/34810 PCT/US00/30950 .

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cgt Arg	atg Met	ggt Gly	aaa Lys	ggt Gly 85	aaa Lys	ggt Gly	aac Asn	gtg Val	gag Glu 90	tat Tyr	tgg Trp	gtt Val	gcc Ala	ttg Leu 95	att Ile	288
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gcc Ala	cgt Arg	gaa Glu 115	gca Ala	ttc Phe	aag Lys	ctg Leu	gca Ala 120	gca Ala	gcg Ala	aaa Lys	ctg Leu	ccg Pro 125	att Ile	aaa Lys	acc Thr	384
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85	90	0 .	95
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gaa atc gca cgt acc ga Glu Ile Ala Arg Thr Gl 165	a tgg tac cgc ga u Trp Tyr Arg Gl 17	u Gly Arg Val Pro	ctg cac 528 Leu His 175
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ctg gat att ttg acc ta Leu Asp Ile Leu Thr Ty 35	c acc aac aag aa r Thr Asn Lys Ly 40	a gcg gct gta ctg vs Ala Ala Val Leu 45	gtc aag 144 Val Lys

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gac att gac gat ctg Asp Ile Asp Asp Leu 65	aaa gtt acg Lys Val Thr 70	aaa att ttc gta Lys Ile Phe Val 75	gac gaa ggc ccg Asp Glu Gly Pro 80	240
agc atg aag cgc att Ser Met Lys Arg Ile 85	atg ccg cgt Met Pro Arg	gca aaa ggt cgt Ala Lys Gly Arg 90	gca gat cgc atc g Ala Asp Arg Ile 95	288
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act tgg tcc cgt cgt Thr Trp Ser Arg Arg 35	tca acg atc Ser Thr Ile 40	Phe Pro Asn Me	g atc ggt ttg acc t Ile Gly Leu Thr 45	144
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gaa atg gtt ggt cac Glu Met Val Gly His 65	aaa ctg ggt Lys Leu Gly 70	gaa ttc gca cc Glu Phe Ala Pro 75	g act cgt act tat o Thr Arg Thr Tyr 80	240
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ccg Pro	aaa Lys 130	act Thr	aag Lys	ctg Leu	ctg Leu	gca Ala 135	cag Gln	aaa Lys	ctg Leu	aaa Lys	gac Asp 140	atg Met	gct Ala	ctg Leu	gaa Glu	432
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agc Ser	gtt Val	gaa Glu	ctg Leu 100	ttt Phe	gct Ala	gac Asp	gtt Val	aaa Lys 105	aaa Lys	gtt Val	gac Asp	gta Val	act Thr 110	ggc Gly	acc Thr	336
tct Ser	aaa Lys	ggt Gly 115	aaa Lys	ggt Gly	ttc Phe	gca Ala	ggt Gly 120	Thr	gtt Val	aag Lys	cgc Arg	tgg Trp 125	aac Asn	ttc Phe	cgt Arg	384
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gto Val	ccg Pro	ggt Gly 195	Ala	acc Thr	ggt Gly	ago Ser	gac Asp 200	Leu	ato Ile	gtt Val	aaa Lys	cca Pro 205	Ala	gto Val	g aag Lys	624

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				tta aaa act Leu Lys Thr		
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aat cac gtg Asn His Val 355	gca gac aa Ala Asp As	t gtg ttg n Val Leu 360	Leu Glu	aac ggt ggt Asn Gly Gly 365	cat tta gac His Leu Asp	1104
				att att aaa Ile Ile Lys 380		
	Val Leu T			gat gcg acc Asp Ala Thr 395		•
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aat ggt ggc Asn Gly Gly	aca cag a Thr Gln A 420	it att aat in Ile Asr	aat tat Asn Tyr 425	ggc ata gcc Gly Ile Ala	aca ggc acc Thr Gly Thr 430	1296
aat atc aac Asn Ile Asn 435	Ser Gly T	g caa aat ar Gln Asr 440	lle Lys	agc ggc ggg Ser Gly Gly 445	aaa gct gac Lys Ala Asp	1344
aca aca att Thr Thr Ile 450	ata tcc to	er ggg ago er Gly Ser 455	cgg cag Arg Gln	gtt gtt gag Val Val Glu 460	aaa gat ggt Lys Asp Gly	1392
	Gly Ser A			ggc tcg ctg Gly Ser Leu 475		•
acc ggc ggt Thr Gly Gly	att gca c Ile Ala H 485	at ggg gtt .s Gly Val	aac cag Asn Gln 490	gag acg ggc Glu Thr Gly	agt gct tta Ser Ala Leu 495	1488
gtt gcc aac Val Ala Asn	acg ggt g Thr Gly A	ca ggg act la Gly Thi	gat atc Asp Ile	gaa gga tac Glu Gly Tyr	aac aag cto Asn Lys Leu	1536

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acc Thr 545	att Ile	gat Asp	act Thr	ggc Gly	ggt Gly 550	aag Lys	ctg Leu	att Ile	gtc Val	cag Gln 555	aag Lys	gag Glu	gct Ala	aaa Lys	aca Thr 560		1680
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ggt Gly	gag Glu	gct Ala	aag Lys 580	cat His	gtt Val	gag Glu	caa Gln	caa Gln 585	tcc Ser	ggc Gly	ggc Gly	gca Ala	tta Leu 590	att Ile	gct Ala	ů.	1776
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act Thr	gaa Glu 690	gca Ala	aat Asn	atc Ile	gaa Glu	agt Ser 695	ggt Gly	gaa Glu	caa Gln	att Ile	gtt Val 700	gat Asp	ggt Gly	GJ À âàà	tca Ser		2112
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aat Asn	atc Ile	ctg Leu	ctg Leu 820	gca Ala	aat Asn	ggc Gly	ggc Gly	gtg Val 825	tta Leu	acc Thr	gtg Val	gag Glu	tca Ser 830	gac Asp	acc Thr	2496
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980 985 990

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cg Ar	g A	at .sp	aat Asn	gtt Val	acg Thr 1049	Pro	gtt Val	aaa Lys	ctc Leu	gaa Glu 1050	Gly	gcg Ala	gtc Val	cgg Arg	att Ile 105	Thr	3168
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L	aa a ys T 185	aca Thr	Gly ggg	gga Gly	GJA	gat Asp 119	Ala	tcg Ser	ttt Phe	acg Thr	ctg Leu 119	Gly	aat Asn	acc Thr	ggc Gly	ggt Gly 1200	3600
t <sup>r</sup>	tc g he V	gtt Val	gat Asp	ctt Leu	ggg Gly 120	Thr	tat Tyr	gag Glu	tat Tyr	gtc Val 121	Leu	aaa Lys	agt Ser	gac Asp	ggc Gly 121	aac Asn 5	3648
a S	gc a er <i>F</i>	aac Asn	tgg Trp	aac Asn	ctg Leu	acc Thr	aat Asn	gat Asp	gtc Val	aaa Lys	ccc Pro	aac Asn	ccg Pro	gac Asp	ccc	atc Ile	3696

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aaa cgc att acg cc Lys Arg Ile Thr Pr 1265	t tot acg gca o o Ser Thr Ala i 1270	gcc gta ctc aat a Ala Val Leu Asn M 1275	tg gca gca aca 38 et Ala Ala Thr 1280	340
tta ccg ttg gta tt Leu Pro Leu Val Ph 12	e Asp Ala Glu	cta aac agt att c Leu Asn Ser Ile A 1290	gc gag cgg ttg 38 rg Glu Arg Leu 1295	388
aac ata atg aaa gc Asn Ile Met Lys Al 1300	a Ser Pro His	aac aat aat gtc t Asn Asn Asn Val T 1305	gg ggg gcg acg 39 rp Gly Ala Thr 1310	936
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ctg ggc ggc tat gc Leu Gly Gly Tyr Al 1380	c agt tgg gaa a Ser Trp Glu	cat gaa agt ggt t His Glu Ser Gly P 1385	tc tat ctg gac 4: The Tyr Leu Asp 1390	176
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ggt cac att gaa ac Gly His Ile Glu Th 1425	c ggg atg cga r Gly Met Arg 1430	ttt acc gat ggt a Phe Thr Asp Gly A 1435		320
acg ccg tat gca to Thr Pro Tyr Ala Se 14	g tta acg ggg r Leu Thr Gly 45	ttc acc gct gat a Phe Thr Ala Asp A 1450	ac ccc gaa tat 4. Asn Pro Glu Tyr 1455	368
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1470 1465 1460 tat cgt gaa ctg ggc gca acg ctg agt tac aac atg cgt ctg ggg aac 4464 Tyr Arg Glu Leu Gly Ala Thr Leu Ser Tyr Asn Met Arg Leu Gly Asn 1475 ggt atg gaa gtt gag ccg tgg ctg aag gcg gct gtg cgc aaa gaa ttt 4512 Gly Met Glu Val Glu Pro Trp Leu Lys Ala Ala Val Arg Lys Glu Phe 1495 1490 gtc gat gat aac cgg gtg aaa gtg aat agt gac ggt aat ttc gtc aat 4560 Val Asp Asp Asn Arg Val Lys Val Asn Ser Asp Gly Asn Phe Val Asn 1515 tat ttg tcg ggc aga cgt gga ata tac cag gca ggt att aaa gcc tca 4608 Tyr Leu Ser Gly Arg Arg Gly Ile Tyr Gln Ala Gly Ile Lys Ala Ser 1530 1525 ttc agc agt acg tta agc ggg cat ctt ggg gtg ggg tat agc cat agt 4656 Phe Ser Ser Thr Leu Ser Gly His Leu Gly Val Gly Tyr Ser His Ser 1545 gcc ggt gtg gaa tcc ccg tgg aac gcg gta gct ggt gtg aac tgg tcg 4704 Ala Gly Val Glu Ser Pro Trp Asn Ala Val Ala Gly Val Asn Trp Ser 1560 1555 4710 ttc tga Phe \* <210> 142 <211> 117 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(117) <400> 142 48 atg aaa gtt cgt gct tcc gtc aag aaa tta tgc cgt aac tgc aaa atc Met Lys Val Arg Ala Ser Val Lys Lys Leu Cys Arg Asn Cys Lys Ile 10 gtt aag cgt gat ggt gtc atc cgt gtg att tgc agt gcc gag ccg aag 96 Val Lys Arg Asp Gly Val Ile Arg Val Ile Cys Ser Ala Glu Pro Lys 30 20 117 cat aaa cag cgc caa ggc tga His Lys Gln Arg Gln Gly \* 35 <210> 143 <211> 1332 <212> DNA <213> Escherichia coli

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gta Val	atg Met 370	Thr	cgc Arg	ctg Leu	acc Thr	ctg Leu 375	gtt Val	ggt Gly	gcg Ala	ctg Leu	tat Tyr 380	Ile	acc Thr	ttt Phe	atc Ile	1152
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atg Met	gct Ala	caa Gln	gtg Val 420	Gln	act Thr	ctg Leu	atg Met	atg Met 425	Ser	: agt : Ser	cag Gln	tat Tyr	gag Glu 430	Ser	gca Ala	1296
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cgt Arg	ggt Gly	cac His 35	aaa Lys	ggt Gly	cag Gln	aag Lys	tct Ser 40	cgt Arg	tct Ser	ggc Gly	ggt Gly	ggc Gly 45	gta Val	cgt Arg	cgc Arg	144
ggt Gly	ttc Phe 50	gag Glu	ggt Gly	ggt Gly	cag Gln	atg Met 55	cct Pro	ctg Leu	tac Tyr	cgt Arg	cgt Arg 60	ctg Leu	ccg Pro	aaa Lys	ttc Phe	192
ggc Gly 65	ttc Phe	act Thr	tct Ser	cgt Arg	aaa Lys 70	gca Ala	gcg Ala	att Ile	aca Thr	gcc Ala 75	gaa Glu	att Ile	cgt Arg	ctg Leu	tct Ser 80	24
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gcg Ala	gct Ala	aac Asn	att Ile 100	atc Ile	ggt Gly	atc Ile	cag Gln	atc Ile 105	gag Glu	ttc Phe	gcg Ala	aaa Lys	gtg Val 110	Ile	ctg Leu	33
gct Ala	ggc Gly	gaa Glu 115	Val	acg Thr	act Thr	ccg Pro	gta Val 120	act Thr	gtt Val	cgt Arg	ggc	ctg Leu 125	cgt Arg	gtt Val	act Thr	38
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taa *																43
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ggt Gly	cac His	acc Thr 35	gta Val	gag Glu	cgc Arg	gag Glu	gat Asp 40	act Thr	cct Pro	gct Ala	att Ile	cgc Arg 45	ggt Gly	atg Met	atc Ile	144
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gcg Ala	gta Val	aac Asn	cgc Arg 20	gta Val	tct Ser	aaa Lys	acc Thr	gtt Val 25	aaa Lys	ggt Gly	ggt Gly	cgt Arg	att Ile 30	Pne	tcc Ser	96
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ctg Leu	caa Gln	cac His	cct	gtt Val 85	Lys	ggt Gly	gtt Val	cac His	acg Thr	Gly	tct Ser	cgc Arg	gta Val	tto Phe 95	atg Met	288
caq Gln	g ccg Pro	gct Ala	tcc Ser 100	Glu	ggt Gly	acc	ggt	ato / Ile 105	: Ile	gcc Ala	ggt Gly	ggt Gly	gca Ala 110	Met	cgc Arg	336
gco Ala	gtt Val	ctg Leu 115	Glu	gto Val	gct Ala	ggg	gtt Val 120	His	aac Asr	gtt Val	cto Leu	g gct Ala 125	гра	gco Ala	tat Tyr	384
ggt Gl	tcc Ser 130	Thr	aac Asr	ccg Pro	atc Ile	aac Asn 135	va:	g gtt L Val	cgt L Arc	g Ala	a act a Thi 140	c Ile	gat Asp	ggo Gl	c ctg / Leu	432

gaa aat atg Glu Asn Met 145	aat tct Asn Ser	cca gad Pro Gla 150	a atg 1 Met	gtc Val	gct Ala	gcc Ala 155	aag Lys	cgt Arg	ggt Gly	aaa Lys	tcc Ser 160	480
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cgt cac att Arg His Ile 35	Tyr Ala	cag gt Gln Va	a att l Ile 40	Ala	ccg Pro	aac Asn	ggt Gly	tct Ser 45	gaa Glu	gtt Val	ctg Leu	144
gta gct gct Val Ala Ala 50	tct act Ser Thr	gta ga Val Gl	u Lys	gct Ala	atc Ile	gct Ala	gaa Glu 60	caa Gln	ctg Leu	aag Lys	tac Tyr	192
acc ggt aac Thr Gly Asn 65	aaa gad Lys Asp	gcg gc Ala Al 70	t gca a Ala	gct Ala	gtg Val	ggt Gly 75	aaa Lys	gct Ala	gtc Val	gct Ala	gaa Glu 80	240
cgc gct ctg Arg Ala Leu	gaa aaa Glu Lys 85	Gly Il	c aaa e Lys	gat Asp	gta Val 90	tcc Ser	ttt Phe	gac Asp	cgt Arg	tcc Ser 95	ggg	288
ttc caa tat Phe Gln Tyr	cat ggt His Gly 100	cgt gt Arg Va	c cag l Gln	gca Ala 105	Leu	gca Ala	gat Asp	gct Ala	gcc Ala 110	cgt Arg	gaa Glu	336
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ctg Leu	act Thr	cgt Arg 35	act Thr	ctc Leu	aac Asn	gat Asp	gct Ala 40	gtt Val	gaa Glu	gtt Val	aaa Lys	cat His 45	gca Ala	gat Asp	aat Asn	144
acc Thr	ctg Leu 50	acc Thr	ttc Phe	ggt Gly	ccg Pro	cgt Arg 55	gat Asp	ggt Gly	tac Tyr	gca Ala	gac Asp 60	ggt Gly	tgg Trp	gca Ala	cag Gln	192
gct Ala 65	ggt Gly	acc Thr	gcg Ala	cgt Arg	gcc Ala 70	ctg Leu	ctg Leu	aac Asn	tca Ser	atg Met 75	gtt Val	atc Ile	ggt Gly	gtt Val	acc Thr 80	240
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gcg Ala	gtt Val	aaa Lys	ggc Gly 100	aat Asn	gtg Val	att Ile	aac Asn	ctg Leu 105	tct Ser	ctg Leu	ggt Gly	ttc Phe	tct Ser 110	cat His	cct Pro	336
gtt Val	gac Asp	cat His 115	cag Gln	ctg Leu	cct Pro	gcg Ala	ggt Gly 120	atc Ile	act Thr	gct Ala	gaa Glu	tgt Cys 125	ccg Pro	act Thr	cag Gln	384
act Thr	gaa Glu 130	atc Ile	gtg Val	ctg Leu	aaa Lys	ggc Gly 135	gct Ala	gat Asp	aag Lys	cag Gln	gtg Val 140	atc Ile	ggc	cag Gln	gtt Val	432
gca Ala 145	gcg Ala	gat Asp	ctg Leu	cgc Arg	gcc Ala 150	tac Tyr	cgt Arg	cgt Arg	cct Pro	gag Glu 155	cct Pro	tat Tyr	aaa Lys	Gly	aag Lys 160	480
ggt Gly	gtt Val	cgt Arg	tac Tyr	gcc Ala 165	gac Asp	gaa Glu	gtc Val	gtg Val	cgt Arg 170	acc	aaa Lys	gag Glu	gct Ala	aag Lys 175	aag Lys	528
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aa ys	gtg Val	gca Ala 35	atc Ile	gcc Ala	aac Asn	gtg Val	ctg Leu 40	aag Lys	gaa Glu	gaa Glu	ggt Gly	ttt Phe 45	att Ile	gaa Glu	gat Asp	144
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ca	ggt Gly	ctg Leu	cgc Arg	atc Ile 85	tat Tyr	aaa Lys	cgt Arg	aaa Lys	gat Asp 90	gag Glu	ctg Leu	ccg Pro	aaa Lys	gtt Val 95	atg Met	288
cg la	ggt Gly	ctg Leu	ggt Gly 100	atc Ile	gca Ala	gtt Val	gtt Val	tct Ser 105	acc Thr	tct Ser	aaa Lys	ggt Gly	gtt Val 110	atg Met	act Thr	336
at sp	cgt Arg	gca Ala 115	gcg Ala	cgc Arg	cag Gln	gct Ala	ggt Gly 120	Leu	ggt Gly	ggc Gly	gaa Glu	att Ile 125	atc Ile	tgc Cys	tac Tyr	384
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gct Ala	gat Asp	aaa Lys	tac Tyr 20	Phe	gcç Ala	g aaa a Lys	a cgo	g gct g Ala 25	ı Glı	a cto ı Leu	g aaa 1 Lys	a gco	ato 11e 30	5 TT6	c tct e Ser	96
gat Asp	gte Val	g aad L Asi 39	n Ala	tco Ser	c gad	c gaa o Glu	a gat ı Asp 40	Arg	tg:	g aad o Asi	e get n Ala	t gtt a Val	. Let	c aac u Ly:	g ctg s Leu	144

cag act ctg Gln Thr Leu 50	ccg cgt gat Pro Arg Asp	tcc agc ( Ser Ser )	ccg tct Pro Ser	cgt cag Arg Gln 60	cgt aac Arg Asn	cgc tgc Arg Cys	192
cgt caa aca Arg Gln Thr 65	ggt cgt ccg Gly Arg Pro 70	His Gly	ttc ctg Phe Leu	cgg aag Arg Lys 75	ttc ggg Phe Gly	ttg agc Leu Ser 80	240
cgt att aag Arg Ile Lys	gtc cgt gaa Val Arg Glu 85	gec get a	atg cgc Met Arg 90	ggt gaa Gly Glu	atc ccg Ile Pro	ggt ctg Gly Leu 95	288
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aag atc acc Lys Ile Thr 35	ctg aac atg Leu Asn Met	ggt gtt Gly Val 40	ggt gaa Gly Glu	gcg atc Ala Ile	gct gac Ala Asp 45	aaa aaa Lys Lys	144
ctg ctg gat Leu Leu Asp 50	aac gca gca Asn Ala Ala	gca gac Ala Asp 55	ctg gca Leu Ala	gca atc Ala Ile 60	tcc ggt Ser Gly	caa aaa Gln Lys	192
ccg ctg atc Pro Leu Ile 65		Arg Lys					240
cag ggc tat Gln Gly Tyr	ccg atc ggc Pro Ile Gly 85	tgt aaa Cys Lys	gta act Val Thr 90	ctg cgt Leu Arg	ggc gaa Gly Glu	cgc atg Arg Met 95	288
tgg gag ttc Trp Glu Phe	ttt gag cgc Phe Glu Arc 100 ·	Leu Ile	act att Thr Ile 105	gct gta Ala Val	cct cgt Pro Arg 110	atc cgt Ile Arg	336
gac ttc cgt Asp Phe Arg 115	ggc ctg tcc Gly Leu Scr	gct aag Ala Lys 120	tct ttc Ser Phe	gac ggt Asp Gly	cgt ggt Arg Gly 125	aac tac Asn Tyr	384

agc atg ggt gtc cgt Ser Met Gly Val Arg 130		Ile Phe Pro G		
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aaa tct gac gaa gaa Lys Ser Asp Glu Glu 165	ggc cgc gct Gly Arg Ala	ctg ctg gct g Leu Leu Ala A 170	gcc ttt gac ttc Ala Phe Asp Phe 175	ccg 528 Pro
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aaa gat aaa ggt aaa Lys Asp Lys Gly Lys 20				
aag gtc att gtt gaa Lys Val Ile Val Glu 35	ggt atc aac Gly Ile Asn 40	ctg gtt aag a Leu Val Lys I	aaa cat cag aag Lys His Gln Lys 45	ccg 144 Pro
gtt ccg gcc ctg aac Val Pro Ala Leu Asn 50	caa ccg ggt Gln Pro Gly 55	ggc atc gtt of Gly Ile Val	gaa aaa gaa gcc Glu Lys Glu Ala 60	gct 192 Ala
att cag gtt tcc aac Ile Gln Val Ser Asn 65				
gac cgt gta ggc ttt Asp Arg Val Gly Phe 85	Arg Phe Glu	gac ggt aaa a Asp Gly Lys I 90	aaa gtc cgt ttc Lys Val Arg Phe 95	ttc 288 Phe
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cgt ggt aa Arg Gly Ly 50										192
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ggt aat gc Gly Asn Al										288
acg cgt at Thr Arg Il										336
atg aaa at Met Lys Il 11	e Ile						taa *			372
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	ggt Gly 50															192
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gat Asp	ggc Gly	cct Pro	gac Asp	att Ile 85	atc Ile	ttc Phe	tgg Trp	gca Ala	cac His 90	gac Asp	cgc Arg	ttt Phe	ggt Gly	ggc Gly 95	tac Tyr	288
	caa Gln															336
	aag Lys															384
	att Ile 130															432
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	caa Gln															576
	gcg Ala															624
gtg Val	gat Asp 210	aac Asn	gct Ala	ggc Gly	gcg Ala	aaa Lys 215	gcg Ala	ggt Gly	ctg Leu	acc Thr	ttc Phe 220	ctg Leu	gtt Val	gac Asp	ctg Leu	672
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	ccg Pro															864

Ser Ala Gly Ile Asn Ala Ala Ser Pro Asn Lys Glu Leu Ala Lys Glu 290 295 300	912
Phe Leu Glu Asn Tyr Leu Leu Thr Asp Glu Gly Leu Glu Ala Val Asn 305 310 315 320	960
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					aaa Lys										384
_				-	gcg Ala		-	_		-					432
		_	_		aaa Lys 150						-		-		480
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					gcg Ala										576
				_	atg Met	_		_	_	_			_	_	624
					gac Asp										672
				.=	ccg Pro 230							_			720
					tgg Trp										768
					aaa Lys										816
					ctc Leu										864
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PCT/US00/30950 WO 01/34810

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aaa ggg Lys Gl	g ttg / Leu	ttt Phe 340	aac Asn	cag Gln	agc Ser	ttc Phe	ggt Gly 345	gaa Glu	atc Ile	aac Asn	atg Met	atg Met 350	ttg Leu	agc Ser		1056
gcg cto Ala Le	ttt Phe 355	ggc	gtg Val	aag Lys	ccc Pro	gcc Ala 360	tgg Trp	ttc Phe	agc Ser	gat Asp	ccg Pro 365	acc Thr	acc Thr	gcc Ala		1104
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<220>

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Ala Ala Ile Thr 225	Glu Val Pr 230	val Ala Se	r Leu Leu Leu 235	Arg Asp Val 240	
aac agc tac acc Asn Ser Tyr Thr	ctg gcc gt Leu Ala Va 245	g ggg atg ca Gly Met Gl 25	n Gln Tyr Leu	aac ccg caa 768 Asn Pro Gln 255	
aac tac ctg tgg Asn Tyr Leu Trp 260	ggt gac tt Gly Asp Ph	gee gee ge Ala Ala Al 265	t gcc gtg atg a Ala Val Met	tct gca tta 816 Ser Ala Leu 270	
ccg atc acc atc Pro Ile Thr Ile 275	gtc ttc tt Val Phe Le	g ctg gct ca 1 Leu Ala Gl 280	a cgc tgg ctg n Arg Trp Leu 285	gtc aac ggc 864 Val Asn Gly	
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acc aat aaa atc Thr Asn Lys Ile 35					
cac att gcg gcg His Ile Ala Ala 50	gtg acc tt Val Thr Ph	e Thr Asn Ly	a gca gcg cgc s Ala Ala Arg 60	gag atg aaa 192 Glu Met Lys :	
gag cgt gta ggg Glu Arg Val Gly 65	cag acg ct Gln Thr Le 70	g ggg cgc aa u Gly Arg Ly	a gag gcg cgt vs Glu Ala Arg 75	ggg ctg atg 240 Gly Leu Met 80	
atc tcc act ttc Ile Ser Thr Phe	cat acg tt His Thr Le 85	u Gly Leu As	et atc atc aaa op Ile Ile Lys 00	cgc gag tat 288 Arg Glu Tyr 95	•
gcg gcg ctt ggg Ala Ala Leu Gly 100	Met Lys Al	g aac ttc to a Asn Phe Se 105	eg ttg ttt gac er Leu Phe Asp	gat acc gat 336 Asp Thr Asp 110	
cag ctt gct ttg Gln Leu Ala Leu	ctt aaa ga	g ttg acc ga	ng ggg ctg att nu Glv Leu Ile	gaa gat gac 384	

		115					120					125				
	gtt Val 130		_			-		-						_		432
_	ctc Leu			_				_	-	_						480
_	cgt Arg			-		_			_		-	_		_		528
_	tgt Cys		_		-		_	_	_			_	_	_	_	576
_	ctg Leu		_		_	_	_	_	-	_		_				624
_	tat Tyr 210	_	-		_			_	_				_	_		672
	ctg Leu															720
	gac Asp	-	_	-	_					_		_	_	_		768
	ctg Leu		-	-	_	_	-		-		_	-			-	816
	gag Glu	-			_				_		_					864
	ctg Leu 290			_	_	_			_,		_	_	_		_	912
	ctg Leu															960
	cat His															1008
	aat Asn															1056
	cag Gln	-				-			-	_			-		_	1104

-66-

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gac ttg (Asp Leu )	ctg gct Leu Ala	tat ctg Tyr Leu 390	cgc (	gtg o Val I	ctg Leu	act Thr	aac Asn 395	ccg Pro	gac Asp	gat Asp	gac Asp	agc Ser 400	1200
gca ttt ( Ala Phe 1					Pro								1248
acg ctg a				Trp A									1296
ttt acc o		-	Met (		_	_	_	-		_		-	1344
ggt tat of Gly Tyr ( 450													1392
cgt ctg o Arg Leu 1 465													1440
ggc atg ( Gly Met )	-	-		_	Fyr	_		_		_	-		1488
gcc gcc ( Ala Ala (		_	_	Asn V	-			_		_		_	1536
acg gag a Thr Glu !			Ser (	_	_	_		_	-	_			1584
cag gtg ( Gln Val V 530													1632
agt gaa ( Ser Glu ( 545	gaa gag Glu Glu	ctg gat Leu Asp 550	cag ( Gln V	gtg o	caa Gln	ctg Leu	atg Met 555	act Thr	ctc Leu	cac His	gcg Ala	tcg Ser 560	1680
aaa ggg ( Lys Gly 1					Tyr								1728
ttt ttg ( Phe Leu l				Ile A									1776
cgg cgg ( Arg Arg )						_	-	-	_	_	_		1824

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gag ccg Glu Pro 625															1920
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											aca Thr			384
											tca Ser			432
											aac Asn			480 °
											tat Tyr			528
_		-	_	_				-			cct Pro 190			576
											gct Ala			624
_											cag Gln			672
											cag Gln			720
											ata Ile			768
											aag Lys 270			816
		-				_		_	_	_	aat Asn			864
											cat His			912
	_			_	_	_		-			tgc Cys	_	_	960
											agc Ser			1008
	_				-	-	-				tat Tyr 350		-	1056

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gtt gtg gcg tcg g Val Val Ala Ser G 50			_	 192
gac aga aag atg g Asp Arg Lys Met G 65				240
atc tct cct gct g Ile Ser Pro Ala V				 288
ggc ttt atg ctg c Gly Phe Met Leu L 100				 336
ggg gtg atg ggc t Gly Val Met Gly P 115				384

	cgc Arg 130															432
	ccg Pro	-					_		_					_	_	480
	gca Ala															528
	tat Tyr															576
	ccg Pro	-	-			-				_			_			624
	acg Thr 210															672
	ggc Gly															720
_	gtc Val					-	-	-	_				_	_	_	768
gac Asp	aga Arg	atc Ile	tgg Trp 260	gcg Ala	cgc Arg	aag Lys	ctg Leu	ttc Phe 265	ggc Gly	ttc Phe	tct Ser	atc Ile	atc Ile 270	gcc Ala	atc Ile	816
	gcc Ala															864
	acg Thr 290							taa *				,				891
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gca	ggc	act	gta	ttg	ctc	agt	ggc	tgt	aat	tct	gcg	ctg	tta	gat	ccc	96

Ala	Gly	Thr	Val 20	Leu	Leu	Ser	Gly	Cys 25	Asn	Ser	Ala	Leu	Leu 30	Asp	Pro	
	gga Gly															144
	ctg Leu 50	_	-		_	-			_		-	-	-	-		192
	gcc Ala		_				-			-	_	_		-	_	240
	tgg Trp							-	_		_		_	-		288
	tta Leu															336
	ctt Leu															384
	gaa Glu 130		-		_	_								-	_	432
_	ggc Gly		-				-		_		_				_	480
	tac Tyr									_						528
	cgt Arg															576
	cat His															624
	tac Tyr 210															672
	ccg Pro															720
	ccg Pro															768
cct	agc	gaa	tac	aac	cag	gtg	gaa	tat	ttc	tcc	aac	gtg	aaa	cca	gac	816

Pro Ser Glu	Tyr Asn Gl 260	n Val Glu	Tyr Phe 265	Ser Asn	Val Lys 270	Pro Asp	
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gac atg acc Asp Met Thr 290							912
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gcg att gtg Ala Ile Val 65		ı Arg Gly					240
agc cag cag Ser Gln Gln				Ala Gly			288
cac cac tac His His Tyr							336
ttc gtg gcg Phe Val Ala 115	atg cct tt Met Pro Ph	c gtt ato e Val Ile 120	Gly Leu	atg aac Met Asn	ctg gtg Leu Val 125	gtt ccg Val Pro	384
ctg cag atc Leu Gln Ile							432

	130			135					140					
			gtt Val 150											480
		 _	gcg Ala	-				_	-			-		528
_			agt Ser	_		_		-	_					576
			ggt Gly											624
			aag Lys											672
			tgg Trp 230											720
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			cat His											816
-	-		ctg Leu			_				_	-	_		864
			gtt Val											912
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			cgc Arg											1152

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											aac Asn						1248
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											tgg Trp 460						1392
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											gac Asp						1584
ctg Leu	act Thr 530	ggc Gly	gac Asp	ccg Pro	tgg Trp	ggt Gly 535	ggc Gly	cgt Arg	acg Thr	ctg Leu	gag Glu 540	tgg Trp	gca Ala	acc Thr	tct Ser		1632
											ccg Pro						1680
											gaa Glu						1728
											aac Asn						1776
atc Ile	gtc Val	att Ile 595	gca Ala	gct Ala	ttc Phe	tcc Ser	acc Thr 600	atc Ile	ttc Phe	ggt Gly	ttc Phe	gcc Ala 605	atg Met	atc Ile	tgg Trp	•	1824
cat His	atc Ile	tgg Trp	tgg Trp	ctg Leu	gcg Ala	att Ile	gtt Val	ggc Gly	ttc Phe	gca Ala	ggc Gly	atg Met	atc Ile	atc Ile	acc Thr		1872

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	atc Ile														1920
	gaa Glu														1968
_	Gly ggg	_					_								1992
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	cac His		_	_											96
_	atg Met	_	_	_		-				_		-		-	144
-	ctg Leu 50					_			_			_	-		192
	ctg Leu														240
	acc Thr			_		-		_	_					_	288
_	gtt Val				_		_			_			-		336
	G] y ggg														384
	ccg Pro 130														432

-76-

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		ggc ctg acc ago Gly Leu Thr Sen 170	Thr Asn Arg T	_
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		gta cag gtt cto Val Gln Val Leo		
		tca gat gaa ggo Ser Asp Glu Gly 75	Trp Asn Met T	
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-78-

ace aaa att ace acg tat cgt tta cct ccc cgc tgg atg ttc ctg aaa

672

Thr	Lys 210	Ile	Thr	Thr	Tyr	Arg 215	Leu	Pro	Pro	Arg	Trp 220	Met	Phe	Leu	Lys	
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	cgc Arg															768
	att Ile															816
	cgc Arg	_				-			_		-	_	-	_		864
	ggg Gly 290															912
	ccg Pro															960
	tac Tyr															1008
	aaa Lys	_		_	_				_				_			1056
	gaa Glu															1104
	aac Asn 370															1152
	ggt Gly															1200
	att Ile															1248
	ctg Leu															1296
	att Ile															1344
aaa	cgc	gtg	ctg	gag	gca	ggt	ggt	att	tcg	att	ctg	caa	ccg	gat	ctc	1392

Lys Arg Val Leu G 450	Glu Ala Gly 455	Gly Ile Ser	Ile Leu Gln Pro 460	Asp Leu
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gaa gcc tat gac g Glu Ala Tyr Asp V 4				
gca ctg gcg gct t Ala Leu Ala Ala C 500				
ctt cag gaa caa a Leu Gln Glu Gln S 515	Ser Met Gly			
ctc gac ttt gtg a Leu Asp Phe Val I 530				
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290

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atc gtt cac ggc aaa tac gtg cca ggc tcg ccg ctt ccg gct gag gcg
                                                                       96
Ile Val His Gly Lys Tyr Val Pro Gly Ser Pro Leu Pro Ala Glu Ala
             20
gaa ctc tgt gag gag ttt gca acc tcg cgc aac atc atc cgt gag gtg
                                                                      144
Glu Leu Cys Glu Glu Phe Ala Thr Ser Arg Asn Ile Ile Arg Glu Val
         35
ttc cgt tcg ctg atg gcg aag cgg ctg att gaa atg aaa cgt tat cgc
                                                                      192
Phe Arg Ser Leu Met Ala Lys Arg Leu Ile Glu Met Lys Arg Tyr Arg
ggg gcg ttt gtg gca ccg cgt aac cag tgg aat tac ctc gac act gac
                                                                      240
Gly Ala Phe Val Ala Pro Arg Asn Gln Trp Asn Tyr Leu Asp Thr Asp
65
                     70
                                         75
gta ctg caa tgg gtg ctg gaa aat gac tac gac cca cgg ctt atc agt
                                                                      288
Val Leu Gln Trp Val Leu Glu Asn Asp Tyr Asp Pro Arg Leu Ile Ser
                 85
gcc atg agc gaa gtg cga aat ctg gtg gaa ccg gcg att gcc cgt tgg
                                                                      336
Ala Met Ser Glu Val Arg Asn Leu Val Glu Pro Ala Ile Ala Arg Trp
            100
gag cag agc gcg cga ctt cca gcg atc tgg cgc aga ttg aat cgg cgc
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Glu Gln Ser Ala Arg Leu Pro Ala Ile Trp Arg Arg Leu Asn Arg Arg
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tga
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caa ctt agc Gln Leu Ser 35											144
acc tgg atg Thr Trp Met 50		Glu A									192
aag gcg ctg Lys Ala Leu 65	-		_			p Gly	-	-	-		240
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Asn Gly Leu	Lys Lys 85		Val Glu	lle Asp 90	Arg Lys	Ile 1	Leu Ala 95	
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gcc Ala	gga Gly 50	gta Val	gac Asp	tta Leu	gtc Val	gag Glu 55	atc Ile	agc Ser	cct Pro	aac Asn	gcc Ala 60	gag Glu	ccg Pro	ccg Pro	gtt Val	192
tgt Cys 65	cgt Arg	ata Ile	atg Met	gat Asp	tac Tyr 70	ggc Gly	aaa Lys	ttc Phe	ctc Leu	tat Tyr 75	gaa Glu	aag Lys	agc Ser	aag Lys	tct Ser 80	240
tct Ser	aag Lys	gaa Glu	cag Gln	aag Lys 85	aaa Lys	aag Lys	caa Gln	aaa Lys	gtt Val 90	atc Ile	cag Gln	gtt Val	aag Lys	gaa Glu 95	att Ile	288
aaa Lys	ttc Phe	cgt Arg	cct Pro 100	ggt Gly	aca Thr	gat Asp	gaa Glu	ggc Gly 105	gac Asp	tat Tyr	cag Gln	gta Val	aaa Lys 110	ctc Leu	cgc Arg	336
agc Ser	ctg Leu	att Ile 115	cgc Arg	ttt Phe	ctc Leu	gaa Glu	gag Glu 120	ggt Gly	gat Asp	aaa Lys	gcc Ala	aaa Lys 125	atc Ile	acg Thr	ctg Leu	384
cgt Arg	ttc Phe 130	cgc Arg	ggt Gly	cgt Arg	gag Glu	atg Met 135	gcg Ala	cac His	cag Gln	caa Gln	atc Ile 140	ggt Gly	atg Met	gaa Glu	gtg Val	432
		cgc Arg														480
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gct Ala	gta Val	agc Ser	ccc Pro 20	Met	gat Asp	gtt Val	gcg Ala	ctg Leu 25	gac Asp	att Ile	ggt Gly	cca Pro	ggt Gly 30	ctg Leu	gcg Ala	96

	_	_		_	ggg Gly	_				-	-	-				144
-	_		•		gac Asp	-		_	-				-		_	192
					atc Ile 70											240
					ctt Leu											288
-		-			ttt Phe			_	-	-		-	_	-		336
	_	_	-	-	gaa Glu	-			-		_				-	384
					gtc Val											432
-	-			-	aac Asn 150	_			-			-		_		480
_	-			_	cat His	-	_	_			-				-	528
_		•	-	_	tgc Cys	-		_		-	_		_	-		576
_					cta Leu	_		_	_		_			_		624
					atg Met											672
_			_		aac Asn 230	_		-	_	_	_	-	_	-		720
					aaa Lys											768
					ggt Gly											816

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cag Gln	tat Tyr 290	cag Gln	gaa Glu	gtt Val	aaa Lys	ggt Gly 295	ccg Pro	ttc Phe	atg Met	atg Met	gac Asp 300	cgt Arg	gtc Val	ctg Leu	tgg Trp	912	!
gaa Glu 305	aaa Lys	acc Thr	ggt Gly	cac His	tgg Trp 310	gac Asp	aac Asn	tac Tyr	aaa Lys	gat Asp 315	gca Ala	atg Met	ttc Phe	acc Thr	aca Thr 320	960	•
					gaa Glu											1008	ł
cac His	gta Val	caa Gln	att Ile 340	ttc Phe	aac Asn	cag Gln	ggg Gly	ctg Leu 345	aag Lys	tct Ser	tat Tyr	cgc Arg	gat Asp 350	ctg Leu	ccg Pro	1056	j
ctg Leu	cgt Arg	atg Met 355	gcc Ala	gag Glu	ttt Phe	ggt Gly	agc Ser 360	tgc Cys	cac His	cgt Arg	aac Asn	gag Glu 365	ccg Pro	tca Ser	ggt Gly	1104	i
tcg Ser	ctg Leu 370	cat His	ggc Gly	ctg Leu	atg Met	cgc Arg 375	gtg Val	cgt Arg	gga Gly	ttt Phe	acc Thr 380	cag Gln	gat Asp	gac Asp	gcg Ala	1152	2
cat His 385	atc Ile	ttc Phe	tgt Cys	act Thr	gaa Glu 390	gaa Glu	caa Gln	att Ile	cgc Arg	gat Asp 395	gaa Glu	gtt Val	aac Asn	gga Gly	tgt Cys 400	1200	)
atc Ile	cgt Arg	tta Leu	gtc Val	tat Tyr 405	gat Asp	atg Met	tac Tyr	agc Ser	act Thr 410	ttt Phe	ggc	ttc Phe	gag Glu	aag Lys 415	atc Ile	1248	}
gtc Val	gtc Val	aaa Lys	ctc Leu 420	tcc Ser	act Thr	cgt Arg	cct Pro	gaa Glu 425	aaa Lys	cgt Arg	att Ile	ggc Gly	agc Ser 430	gac Asp	gaa Glu	1296	ŝ
atg Met	tgg Trp	gat Asp 435	cgt Arg	gct Ala	gag Glu	gcg Ala	gac Asp 440	ctg Leu	gcg Ala	gtt Val	gcg Ala	ctg Leu 445	gaa Glu	gaa Glu	aac Asn	1344	1
aac Asn	atc Ile 450	Pro	ttt Phe	gaa Glu	tat Tyr	caa Gln 455	ctg Leu	ggt Gly	gaa Glu	ggc	gct Ala 460	ttc Phe	tac Tyr	ggt Gly	ccg Pro	1392	2
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tat Tyr	gta Val	ggc Gly	gaa Glu 500	gac Asp	aat Asn	gaa Glu	cgt Arg	aaa Lys 505	Val	ccg Pro	gta Val	atg Met	att Ile 510	cac His	cgc Arg	1536	5

gca att o Ala Ile I														1584
ttc gct ( Phe Ala ( 530			_					_	-	_	_	-		1632
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aaa cta ( Lys Leu S														1728
aag att ( Lys Ile (		Lys		_				_	-	-	-			1776
atg ctg o														1824
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	gtc Val															288
	gtt Val	_		-	_			_				-		_		336
-	cgt Arg	-			-		-		_						-	384
	gaa Glu 130		_		_	_	-	-		-	_	_	_		_	432
	caa Gln															480
	aag Lys															528
	tcc Ser															576
	ccg Pro															624
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	gca Ala															720
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ggt Gly	acg Thr	caa Gln	act Thr 260	atg Met	acg Thr	gtg Val	tat Tyr	aaa Lys 265	cct Pro	att Ile	acg Thr	ttg Leu	ttg Leu 270	gca Ala	aat Asn	816
	gcc Ala															864
gca	gat	acc	aca	ctg	aat	aat	ggc	ctg	aaa	gat	gtc	ccc	tcc	cgc	ctc	912

Ala	Asp 290	Thr	Thr	Leu	Asn	Asn 295	Gly	Leu	Lys	Asp	Val 300	Pro	Ser	Arg	Leu	
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	atg Met															96
	gca Ala		_	-				-						_		144

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					gcc Ala											624
					ctg Leu											672
					tct Ser 230											720
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					aat Asn											864

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gcg atg atc of Ala Met Ile N		Gly Ser Leu				960
ccg cgg ctg ( Pro Arg Leu (						1008
ttc ggc cat o			-		r Ile Ile	1056
ctg caa ggg g Leu Gln Gly A 355				-		1104
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									gcc Ala							192
			_				_		gat Asp	_			-			240
_		-							tgc Cys 90	-					-	288
	•	-	-	-	-	-			gtt Val		-					336
_		-						_	Gly Ggc		_	-		-		384
									agc Ser							432
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									gat Asp							576
									gaa Glu							624
									att Ile							672
ccg Pro 225	ctg Leu	cgt Arg	ccg Pro	ctg Leu	ggt Gly 230	tac Tyr	aaa Lys	gaa Glu	ggc Gly	att Ile 235	gta Val	acg Thr	ctg Leu	atg Met	gaa Glu 240	720
									gag Glu 250							768

GIY FIO Leu	gag att Glu Ile 260											816
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aaa cag cgt Lys Gln Arg 290	act gac Thr Asp	Asn V	tg atc /al Ile !95	gtc Val	atc (	gat Asp	tac Tyr 300	gcc Ala	gaa Glu	att Ile	tcg Ser	912
caa ggg ctg Gln Gly Leu 305	cac ccg His Pro	tgg c Trp L 310	tg gca eu Ala	ccg Pro	Phe :	ctg Leu 315	atg Met	ttc Phe	gtg Val	cca Pro	atg Met 320	960
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<pre>&lt;221&gt; CDS &lt;222&gt; (1) &lt;400&gt; 176 atg aac gcc Met Asn Ala 1  ggc ccg gca Gly Pro Ala  ggt atg ttt Gly Met Phe</pre>	gct att Ala Ile 5 acg ggc Thr Gly 20 acc tgc Thr Cys agc gag Ser Glu gcg ttc Ala Phe	cgg a Arg I ggc c Gly H ctg g Leu G gcg c Ala P 70 cag a Gln T	Att tac Lie Tyr Cac cag His Gln 40 His Tyr 55 Ccg gac Pro Asp	gca Ala 25 cgg Arg gac Asp tta Leu cag	Trp 10 agg Arg ctg Leu ggc Gly aaa Lys	Asn agt Ser cct Pro atc Ile gcg Ala 75 ccg	tac Tyr att Ile gaa Glu 60 ggc Gly	Asn ccg Pro gaa Glu 45 att Ile ggc Gly atc	Pro atg Met 30 cac His tgg Trp atc Ile	Ser 15 aaa Lys gca Ala ggc Gly aaa Lys	Pro aca Thr ttt Phe ggt Gly caa Gln 80 acg	96 144 192

Pro Glu Thr	Asn Gly 1	Tyr Pro T	Tyr Asn 105	Met Met		Asp Glu 110	His
atg cgt cgc Met Arg Arg 115	gaa agc d Glu Ser I	Leu Asp M	atg atc Met Ile 120	aag ctg Lys Leu	gcg atg q Ala Met A 125	gat atg Asp Met	gca 384 Ala
aaa gag atg Lys Glu Met 130	aac gcg ( Asn Ala (	ggt tat a Gly Tyr T 135	acg ctg Thr Leu	att tcc Ile Ser	gcc ggc o Ala Gly I 140	cca cgc Pro Arg	ggg 432 Gly
cta tct cac Leu Ser His 145		taa *		-			450
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<220> <221> CDS <222> (1)	(384)				,	•	***
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gga tta att Gly Leu Ile 35	act tca a	aaa gta a Lys Val 1	aaa tct Lys Ser 40	cgc ccg Arg Pro	caa tgt Gln Cys 45	tgt gac Cys Asp	gat 144 Asp
gac gcg atg Asp Ala Met 50	atc att	tgc ggg 1 Cys Gly 0 55	tgc atg Cys Met	gcc cgt Ala Arg	ctg aaa l Leu Lys 1	aag aac Lys Asn	aac 192 Asn
agc gat ttg Ser Asp Leu 65	cac gat	tta tta ( Leu Leu 1 70	gta gat Val Asp	tat tat Tyr Tyr 75	gta gtc ( Val Val	ggt atg Gly Met	aca 240 Thr 80
ttc atg tca Phe Met Ser	ctg gca Leu Ala 85	ggt aag ( Gly Lys )	cat tgc His Cys	tgc tct Cys Ser 90	gat ggt Asp Gly	tat atc Tyr Ile 95	ggg 288 Gly
aaa agg tta Lys Arg Leu	cag aag Gln Lys 100	gct gag ( Ala Glu (	ggc ata Gly Ile 105	att gaa Ile Glu	Gly Met	tta atg Leu Met 110	gca 336 Ala
tta gat atc Leu Asp Ile 115		Glu Met					taa 384 *

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gaa ( Glu	gtg Val	cgc Arg 35	atg Met	gcg Ala	ctg Leu	ctg Leu	gag Glu 40	gcg Ala	gac Asp	gta Val	gct Ala	ctg Leu 45	ccg Pro	gta Val	gtg Val	144
cgt (																192
aat Asn 1																240
gaa Glu																288
gcg Ala																336
aaa Lys																384
aag Lys																432
atc Ile 145																480
cct Pro	tct Ser	gat Asp	gtt Val	ggt Gly 165	cag Gln	aag Lys	ccg Pro	gta Val	gat Asp 170	atc Ile	gtt Val	aac Asn	gcg Ala	gcg Ala 175	ctg Leu	528
aaa Lys																576
ggt Gly																624

cat His	gcg Ala 210	tcg Ser	att Ile	aac Asn	ccg Pro	gtt Val 215	gaa Glu	acc Thr	ctg Leu	ttt Phe	gtg Val 220	gtt Val	gac Asp	gcc Ala	atg Met		672
acc Thr 225	ggt Gly	cag Gln	gat Asp	gcg Ala	gcc Ala 230	aat Asn	acg Thr	gca Ala	aaa Lys	gca Ala 235	ttc Phe	aat Asn	gaa Glu	gcg Ala	tta Leu 240		720
ccg Pro	ctt Leu	acc Thr	ggc Gly	gta Val 245	gtg Val	ttg Leu	acc Thr	aaa Lys	gtg Val 250	gac Asp	ggc Gly	gat Asp	gcc Ala	cgc Arg 255	ggc Gly		768
ggt Gly	gcg Ala	gcg Ala	ctc Leu 260	tct Ser	att Ile	cgt Arg	cac His	atc Ile 265	act Thr	ggc Gly	aaa Lys	ccg Pro	atc Ile 270	aag Lys	ttc Phe		816
ctc Leu	ggt Gly	gtt Val 275	ggc Gly	gag Glu	aaa Lys	act Thr	gag Glu 280	gcg Ala	ctg Leu	gag Glu	ccg Pro	ttc Phe 285	cat His	ccg Pro	gac Asp		864
cgc Arg	atc Ile 290	gcg Ala	tcg Ser	cgt Arg	att Ile	ctc Leu 295	ggc Gly	atg Met	ggc Gly	gac Asp	gta Val 300	ct.g Leu	tcg Ser	ctg Leu	atc Ile	٠.	912
gaa Glu 305	gat Asp	atc Ile	gaa Glu	agc Ser	aaa Lys 310	gtt Val	gac Asp	cgc Arg	gcg Ala	cag Gln 315	gca Ala	gag Glu	aaa Lys	tta Leu	gcc Ala 320		960
agc Ser	aag Lys	ctg Leu	aaa Lys	aaa Lys 325	ggt Gly	gac Asp	ggc Gly	ttc Phe	gat Asp 330	ctc Leu	aac Asn	gac Asp	ttt Phe	ctt Leu 335	gag Glu	:	1008
cag Gln	ctg Leu	cgc Arg	cag Gln 340	atg Met	aaa Lys	aat Asn	atg Met	ggc Gly 345	ggc Gly	atg Met	gct Ala	agt Ser	ctg Leu 350	atg Met	ggc Gly		1056
aag L <b>y</b> s	ctg Leu	ccg Pro 355	ggc Gly	atg Met	ggg Gly	cag Gln	atc Ile 360	ccg Pro	gat Asp	aac Asn	gtc Val	aag Lys 365	tca Ser	cag Gln	atg Met		1104
gac Asp	gat Asp 370	aaa Lys	gtg Val	ctg Leu	gtg Val	cgt Arg 375	atg Met	gaa Glu	gcc Ala	atc Ile	atc Ile 380	aac Asn	tcg Ser	atg Met	acg Thr		1152
atg Met 385	Lys	gag Glu	cgc Arg	gct Ala	aag Lys 390	cca Pro	gaa Glu	atc Ile	atc Ile	aaa Lys 395	ggt Gly	tcg Ser	cgt Arg	aaa Lys	cgc Arg 400		1200
cgt Arg	att Ile	gct Ala	gcc Ala	ggt Gly 405	tgc Cys	ggt Gly	atg Met	cag Gln	gtg Val 410	cag Gln	gac Asp	gtt Val	aac Asn	cgt Arg 415	ctt Leu		1248
ctg Leu	aaa Lys	cag Gln	ttc Phe 420	gac Asp	gac Asp	atg Met	cag Gln	cgc Arg 425	atg Met	atg Met	aag Lys	aaa Lys	atg Met 430	aag Lys	aag Lys		1296
ggc Gly	gga Gly	atg Met 435	Ala	aag Lys	atg Met	atg Met	aga Arg 440	agc Ser	atg Met	aag Lys	ggt Gly	atg Met 445	atg Met	ccc Pro	cca Pro		1344

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gac to Asp Le	tg cc eu Pr	c gct o Ala 20	gaa Glu	ttg Leu	cct Pro	ccc Pro	ttg Leu 25	ctg Leu	cgc Arg	cgt Arg	tta Leu	tac Tyr 30	gcc Ala	agc Ser	96
cgg go Arg G	ga gt ly Va 3	l Arg	agt Ser	gcg Ala	caa Gln	gaa Glu 40	ctg Leu	gaa Glu	cgc Arg	agt Ser	gtt Val 45	aaa Lys	ggt Gly	atg Met	144
ctg co Leu P	cc tg ro Tr 50	g cag p Gln	caa Gln	ctg Leu	agc Ser 55	ggc Gly	gtc Val	gaa Glu	aag Lys	gcc Ala 60	gtt Val	gag Glu	atc Ile	ctt Leu	192
tac ac Tyr Ac 65	ac gc sn Al	t ttt a Phe	cgc Arg	gaa Glu 70	gga Gly	acg Thr	cgg Arg	att Ile	att Ile 75	gtg Val	gtc Val	ggt Gly	gat Asp	ttc Phe 80	240
gac g Asp A	cc ga la As	c ggc p Gly	gcg Ala 85	acc Thr	agc Ser	acg Thr	gct Ala	cta Leu 90	agc Ser	gtg Val	ctg Leu	gcg Ala	atg Met 95	cgc Arg	288
tcg c Ser L	tt gg eu Gl	t tgc y Cys 100	agc Ser	aat Asn	atc Ile	gac Asp	tac Tyr 105	ctg Leu	gta Val	cca Pro	aac Asn	cgt Arg 110	ttc Phe	gaa Glu	336
gac g Asp G	gt ta ly Ty 11	r Gly	tta Leu	agc Ser	ccg Pro	gaa Glu 120	gtg Val	gtc Val	gat Asp	cag Gln	gcc Ala 125	cat His	gcc Ala	cgt Arg	384
ggc g Gly A 1	cg ca la Gl 30	g tta n Leu	att Ile	gtc Val	acg Thr 135	gtg Val	gat Asp	aac Asn	ggt Gly	att Ile 140	tcc Ser	tcc Ser	cat His	gcg Ala	432
ggg g Gly V 145	tt ga al Gl	g cac u His	gct Ala	cgc Arg 150	tcg Ser	ttg Leu	ggc Gly	atc Ile	ccg Pro 155	gtt Val	att Ile	gtt Val	acc Thr	gat Asp 160	480
cac c His H	at tt is Le	g cca u Pro	ggc Gly 165	Asp	aca Thr	tta Leu	ccc Pro	gca Ala 170	gcg Ala	gaa Glu	gcg Ala	atc Ile	att Ile 175	aac Asn	528

	cct Pro	aac Asn	ttg Leu	cgc Arg 180	gac Asp	tgt Cys	aat Asn	ttc Phe	ccg Pro 185	tcg Ser	aaa Lys	tca Ser	ctg Leu	gca Ala 190	ggc Gly	gtg Val	576
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	cag Gln	ggc Gly 210	tgg Trp	ttt Phe	gat Asp	gag Glu	cgt Arg 215	aac Asn	atc Ile	gca Ala	att Ile	cct Pro 220	aac Asn	ctg Leu	gca Ala	gaa Glu	672
					gtc Val												720
					cgc Arg 245												768
					cgt Arg												816
:					aaa Lys												864
	cca Pro	cgt Arg 290	ctc Leu	aat Asn	gct Ala	gcc Ala	gga Gly 295	cga Arg	ctg Leu	gac Asp	gat Asp	atg Met 300	tcc Ser	gtc Val	ggt Gly	gtg Val	912
	gcg Ala 305	ctg Leu	ttg Leu	ttg Leu	tgc Cys	gac Asp 310	aac Asn	atc Ile	ggc Gly	gaa Glu	gcg Ala 315	cgc Arg	gtg Val	ctg Leu	gca Ala	aat Asn 320	960
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			_	_	ctg Leu		_	-			_						1056
	acg Thr	cta Leu	ccc Pro 355	ggc Gly	ggg Gly	ctg Leu	gca Ala	atg Met 360	tat Tyr	cac His	ccc Pro	gaa Glu	tgg Trp 365	cat His	cag Gln	ggc Gly	1104
					ctg Leu												1152
					gcg Ala												1200
					ggg Gly 405												1248

		tac Tyr														1296
		ttg Leu 435														1344
		gaa Glu														1392
		gta Val														1440
		cag Gln														1488
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		cgt Arg 515														1584
ctg Leu	ctg Leu 530	gat Asp	ggt Gly	att Ile	gct Ala	ttt Phe 535	aat Asn	gtc Val	gat Asp	acc Thr	gcc Ala 540	ctc Leu	tgg Trp	ccg Pro	gat Asp	1632
aac Asn 545	ggc Gly	gtg Val	cgc Arg	gaa Glu	gtg Val 550	caa Gln	ctg Leu	gct Ala	tat Tyr	aag Lys 555	ctc Leu	gat Asp	atc Ile	aac Asn	gag Glu 560	1680
		ggc Gly														1728
att Ile	tag *															1734
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ttt	gct	cag	gct	gat	gac	gcg	gca	att	caa	caa	acg	tta	gcc	aaa	atg	96

Phe	Ala	Gln	Ala 20	Asp	Asp	Ala	Ala	Ile 25	Gln	Gln	Thr	Leu	Ala 30	Lys	Met	
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aca Thr	gtt Val 50	ctg Leu	act Thr	aac Asn	agc Ser	ggc Gly 55	gtg Val	ttg Leu	tac Tyr	atc Ile	acc Thr 60	gat Asp	gat Asp	ggt Gly	aaa Lys	192
cat His 65	atc Ile	att Ile	cag Gln	ggg Gly	cca Pro 70	atg Met	tat Tyr	gac Asp	gtt Val	agt Ser 75	ggc Gly	acg Thr	gct Ala	ccg Pro	gtc Val 80	240
aat Asn	gtc Val	acc Thr	aat Asn	aag Lys 85	atg Met	ctg Leu	tta Leu	aag Lys	cag Gln 90	ttg Leu	aat Asn	gcg Ala	ctt Leu	gaa Glu 95	aaa Lys	288
gag Glu	atg Met	atc Ile	gtt Val 100	tat Tyr	aaa Lys	gcg Ala	ccg Pro	cag Gln 105	gaa Glu	aaa Lys	cac His	gtc Val	atc Ile 110	acc Thr	gtg Val	336
ttt Phe	act Thr	gat Asp 115	att Ile	acc Thr	tgt Cys	ggt Gly	tac Tyr 120	tgc Cys	cac His	aaa Lys	ctg Leu	cat His 125	gag Glu	caa Gln	atg Met	384
gca Ala	gac Asp 130	tac Tyr	aac Asn	gcg Ala	ctg Leu	ggg Gly 135	atc Ile	acc Thr	gtg Val	cgt Arg	tat Tyr 140	ctt	gct Ala	ttc Phe	ccg Pro	432
cgc Arg 145	Gln	ggg Gly	ctg Leu	gac Asp	agc Ser 150	gat Asp	gca Ala	gag Glu	aaa Lys	gaa Glu 155	atg Met	aaa Lys	gct Ala	atc Ile	tgg Trp 160	480
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agc Ser	gtc Val	gca Ala	cca Pro 180	Ala	agt Ser	tgc Cys	gac Asp	gtg Val 185	Asp	att Ile	gcc Ala	gac Asp	cat His 190	Tyr	gca Ala	576
ctt Leu	ggc Gly	gtc Val 195	Gln	ctt Leu	ggc	gtt Val	agc Ser 200	Gly	act Thr	ccg Pro	gca Ala	gtt Val 205	Val	ctg Leu	agc Ser	624
aat Asn	ggc Gly 210	Thr	ctt Leu	gtt Val	ccg Pro	ggt Gly 215	Tyr	cag Gln	ccg Pro	ccg Pro	aaa Lys 220	Glu	atg Met	aaa Lys	gaa Glu	672
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				gac Asp												192
				gcc Ala												240
				tat Tyr 85												288
				gct Ala												336
				cag Gln												384
cag Gln	cca Pro 130	ctg Leu	gag Glu	cta Leu	cgc Arg	gat Asp 135	aaa Lys	gcc Ala	atg Met	ctt Leu	gaa Glu 140	gtg Val	ttg Leu	tat Tyr	gct Ala	432
	Gly	Leu	Arg	gtc Val	Ser	Glu	Leu	Val	Gly	Leu	Thr	Met	Ser	Āsp	Ile	480
agc Ser	ctg Leu	cgt Arg	cag Gln	ggc Gly 165	gtg Val	gta Val	cgg Arg	gtc Val	att Ile 170	ggt Gly	aaa Lys	ggc Gly	aac Asn	aaa Lys 175	gag Glu	528
cgt Arg	ctg Leu	gtg Val	ccg Pro 180	tta Leu	ggt Gly	gaa Glu	gag Glu	gcg Ala 185	gtt Val	tac Tyr	tgg Trp	ctg Leu	gaa Glu 190	acc Thr	tat Tyr	576
				cgt Arg												624
				cag Gln												672

	215		220	
cac cgt att aaa cat His Arg Ile Lys His 225				
ctg tca ccg cat gtg Leu Ser Pro His Val 245	Leu Arg His			Asn
cat ggt gcg gat tta His Gly Ala Asp Lev 260				_
ctc tcc acc acg cas Leu Ser Thr Thr Glr 275				
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atg ttt ttt aac acc Met Phe Phe Asn Thi 1 5  atg gct ttt agt tca Met Ala Phe Ser Sei	tcg tct att Ser Ser Ile	Thr Ala Leu 10  gcg gac att Ala Asp Ile 25  aaa agt gtc	Cys Phe Val Thr 15 gtc att tcg ggt Val Ile Ser Gly 30 aac gta cgt ctg	Cys act 96 Thr
atg ttt ttt aac acc Met Phe Phe Asn Thr 1 5  atg gct ttt agt tca Met Ala Phe Ser Ser 20  cgc gta ata tat aaa Arg Val Ile Tyr Lys	tcg tct att Ser Ser Ile agc gat caa Ser Asp Gln 40 ccg ttg ctt	Thr Ala Leu 10  gcg gac att Ala Asp Ile 25  aaa agt gtc Lys Ser Val  gtc cag agt	Cys Phe Val Thr 15 gtc att tcg ggt Val Ile Ser Gly 30 aac gta cgt ctg Asn Val Arg Leu 45 tgg tta gat act	Cys  act 96 Thr  gaa 144 Glu  ggc 192
atg ttt ttt aac acc Met Phe Phe Asn Thr 1 5  atg gct ttt agt tcc Met Ala Phe Ser Ser 20  cgc gta ata tat aac Arg Val Ile Tyr Lys 35  aat aaa ggg aat aac Asn Lys Gly Asn Asr	tcg tct att Ser Ser Ile agc gat caa Ser Asp Gln 40 ccg ttg ctt Pro Leu Leu 55	Thr Ala Leu 10  gcg gac att Ala Asp Ile 25  aaa agt gtc Lys Ser Val  gtc cag agt Val Gln Ser  att aca gtc	Cys Phe Val Thr 15 gtc att tcg ggt Val Ile Ser Gly 30 aac gta cgt ctg Asn Val Arg Leu 45 tgg tta gat act Trp Leu Asp Thr 60 cct ttt act gct	Cys  act 96 Thr  gaa 144 Glu  ggc 192 Gly  acg 240
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-103-

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gcg aat caa agc Ala Asn Gln Ser 130	•		-	
ttc tat cgc ccg Phe Tyr Arg Pro 145				_
gcc ctg aag tgg Ala Leu Lys Trp				_
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gaa gct agc ggt Glu Ala Ser Gly 195				
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-	_	agt Ser	-		_		_							_		240
		gtc Val	-		-			-		-	_	_	_			288
		aat Asn		_	_							_				336
-		gcc Ala 115	-	-		-		-	_	-				_		384
	_	acg Thr	-				-	-		_	_		_	-		432
_		cgt Arg	-	_		_	_			_		_	-			480
		aac Asn		_	_		_			-						528
_	-	ttg Leu									-	_				576
-		aat Asn 195	_	_			_	-					_			624
	_	tgg Trp	_	-	_	_	_						_		_	672
		agt Ser			_		-				-	_	-	_		720
		ctg Leu														768
-		ttt Phe	-		-	_		-			_			_	-	816
-	-	atg Met 275	_		_			-	-							864

	gtt Val 290															912
aag Lys 305	att Ile	tat Tyr	gaa Glu	acg Thr	acg Thr 310	gtg Val	ccg Pro	cca Pro	ggc Gly	gct Ala 315	ttc Phe	gtc Val	att Ile	gat Asp	gat Asp 320	960
ctg Leu	agt Ser	ccg Pro	tca Ser	ggg Gly 325	tac Tyr	ggc Gly	agc Ser	gat Asp	ctt Leu 330	att Ile	gtt Val	acc Thr	atc Ile	gaa Glu 335	gaa Glu	1008
	gat Asp															1056
	atg Met															1104
	tta Leu 370															1152
tac Tyr 385	tac Tyr	tac Tyr	ggc Gly	ctg Leu	aat Asn 390	aac Asn	tat Tyr	ctg Leu	acg Thr	ggt Gly 395	tat Tyr	acc Thr	ggt Gly	att Ile	cag Gln 400	1200
	acc Thr															1248
	tca Ser															1296
atc Ile	ccg Pro	gat Asp 435	gat Asp	aaa Lys	aca Thr	tac Tyr	cag Gln 440	GJ Y ggg	caa Gln	agt Ser	tat Tyr	cgt Arg 445	gtt Val	tcc Ser	tgg Trp	1344
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	tat Tyr															1440
	gat Asp															1488
	aat Asn															1536
	ttg Leu															1584

					tgg Trp											1632
					agt Ser 550											1680
cag Gln	cgt Arg	tca Ser	tgg Trp	aat Asn 565	gaa Glu	gac Asp	ggc Gly	gac Asp	act Thr 570	gac Asp	gat Asp	agc Ser	gtt Val	tat Tyr 575	ctt Leu	1728
					att Ile											1776
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aat Asn	aac Asn 610	caa Gln	ctc Leu	aac Asn	gtt Val	agc Ser 615	agc Ser	agt Ser	ggc Gly	tat Tyr	agc Ser 620	gat Asp	aac Asn	gct Ala	cgc Arg	1872
gtc Val 625	agt Ser	tat Tyr	agc Ser	gtg Val	aat Asn 630	act Thr	ggc Gly	tat Tyr	acg Thr	atg Met 635	aat Asn	aaa Lys	gcc Ala	agc Ser	aaa Lys 640	1920
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					att Ile											2016
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					ttt Phe											2112
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gat Asp	cga Arg	tgg Trp	ggt Gly	tat Tyr 725	ggt Gly	gtc Val	acc Thr	agc Ser	gct Ala 730	ctt Leu	tct Ser	cct Pro	tat Tyr	cat His 735	gaa Glu	2208
aac Asn	cgt Arg	atc Ile	gcg Ala 740	ctg Leu	gat Asp	atc Ile	aac Asn	gat Asp 745	ctt Leu	gag Glu	aac Asn	gat Asp	gtt Val 750	gaa Glu	tta Leu	2256
					gta Val											2304

gct gat ttt gaa acc gtg caa ggg caa tca gcc att atg aac atc aca Ala Asp Phe Glu Thr Val Gln Gly Gln Ser Ala Ile Met Asn Ile Thr 770 780	2352
cga agt gat ggt aaa aat att cca ttt gct gca gat att tat gat gag Arg Ser Asp Gly Lys Asn Ile Pro Phe Ala Ala Asp Ile Tyr Asp Glu 785 790 795 800	2400
caa ggc aat gtc att ggt aat gtt gga cag ggt gga caa gca ttt gtt Gln Gly Asn Val Ile Gly Asn Val Gly Gln Gly Gln Ala Phe Val 805 810 815	2448
cgt ggt att gag cag cag gga aat atc agc att aaa tgg ctc gaa caa Arg Gly Ile Glu Gln Gln Gly Asn Ile Ser Ile Lys Trp Leu Glu Gln 820 825 830	2496
agt aaa ccc gta agt tgt ctt gcg cat tat caa caa agc cca gaa gca Ser Lys Pro Val Ser Cys Leu Ala His Tyr Gln Gln Ser Pro Glu Ala 835 840 845	2544
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Gly	Arg	Lys	Ile	Asn 85	Lys	Arg	Glu	Trp	Ala 90	Gly	Asn	Ala	Ser	Ala 95	Trp		
			ccg Pro 100													33	6
			gta Val													38	4
			aat Asn													43	2
			gaa Glu			Val										48	0
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aaa Lys	ggc Gly	cag Gln 195	cgg Arg	ctg Leu	ttt Phe	ctg Leu	ttt Phe 200	cgc Arg	aat Asn	aaa Lys	ttt Phe	gtc Val 205	cac His	agc Ser	ggc Gly	62	<b>!4</b>
agt Ser	ggc Gly 210	aaa Lys	aac Asn	gag Glu	att Ile	ttt Phe 215	tta Leu	atc Ile	tgt Cys	tcc Ser	ggc Gly 220	acc Thr	gac Asp	att Ile	acc Thr	67	12
gaa Glu 225	gag Glu	cgc Arg	cgc Arg	gct Ala	cag Gln 230	gag Glu	cga Arg	ctg Leu	cgt Arg	att Ile 235	ctg Leu	gca Ala	aat Asn	acc Thr	gac Asp 240	72	20
agt Ser	atc Ile	acc Thr	gga Gly	ctg Leu 245	ccg Pro	aat Asn	cgt Arg	aac Asn	gca Ala 250	atg Met	cag Gln	gat Asp	tta Leu	atc Ile 255	gat Asp	7 (	68
cac His	gct Ala	att Ile	aat Asn 260	cat His	gca Ala	gat Asp	aac Asn	aat Asn 265	aaa Lys	gtt Val	ggg Gly	gtt Val	gtg Val 270	tat Tyr	ctt Leu	8:	16
gat Asp	ttg Leu	gat Asp 275		ttc Phe	aaa Lys	aag Lys	gtc Val 280	Asn	gac Asp	gcc	tat Tyr	ggg Gly 285	His	ttg Leu	ttt Phe	81	64
ggt Gly	gac Asp 290	Gln	tta Leu	tta Leu	cgc Arg	gac Asp 295	Val	tca Ser	ttg Leu	gct Ala	att Ile 300	Leu	agc Ser	tgt Cys	ctc		12
gaa Glu 305	His	gac Asp	cag Gln	gtg Val	ttg Leu 310	Ala	cgt	cca Pro	ggt Gly	ggg Gly 315	Asp	gag Glu	ttt Phe	ctg Leu	gta Val 320	9	60
ctg	gca	tco	aac	acc	tca	caa	ago	gcg	ctg	gaa	gca	ato	gca	tca	cga	10	08

Leu	Ala	Ser	Asn	Thr 325	Ser	Gln	Ser	Ala	Leu 330	Glu	Ala	Met	Ala	Ser 335	Arg		
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	cgg Arg															1248	3
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	cgt Arg 450															139	2
	ggg Gly															144	0
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:	85	90		95	
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acg atc cct tcg g Thr Ile Pro Ser V 115	ta gat aaa al Asp Lys	aat gca ttg Asn Ala Leu 120	aac ggc agg a Asn Gly Arg A 125	aat gtt ttg Asn Val Leu	384
caa ctg gcg att t Gln Leu Ala Ile L 130	ta tcg cgc eu Ser Arg 135	atg aaa tta Met Lys Leu	ttt ctc cgt o Phe Leu Arg 1 140	cca att caa Pro Ile Gln	432
tta caa gaa tta c Leu Gln Glu Leu P 145	cc gca gaa ro Ala Glu 150	gcg ccg gac Ala Pro Asp	aca ctc aag Thr Leu Lys 155	ttt tcg cga Phe Ser Arg 160	
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aag ctg aaa ttt c Lys Leu Lys Phe G 210	ag acc gtt In Thr Val 215	aat gat tat Asn Asp Tyr	ggt tca gta ( Gly Ser Val ' 220	act ccg gtc Thr Pro Val	672
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	ctc Leu 450															1392
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					gtt Val											2064
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att acc gtt acc cag ggc gga aaa ccg gtg ccg ttt gga tca ctg g Ile Thr Val Thr Gln Gly Gly Lys Pro Val Pro Phe Gly Ser Leu V 785 790 795	gta 2400 Val 800
cgg gaa aac agt acc gga ata acc agt atg gtg ggt gat gac ggg c Arg Glu Asn Ser Thr Gly Ile Thr Ser Met Val Gly Asp Asp Gly G 805 810 815	caa 2448 Gln
gtt tat tta agt ggt gcg cca ttg tct ggt gaa tta ctg gtt cag t Val Tyr Leu Ser Gly Ala Pro Leu Ser Gly Glu Leu Leu Val Gln 7 820 825 830	tgg 2496 Trp
gga gac ggc gcg aac tca cgc tgc att gcg cac tat gta ttg ccg a Gly Asp Gly Ala Asn Ser Arg Cys Ile Ala His Tyr Val Leu Pro I 835 840 845	aag 2544 Lys
caa agc tta cag caa gcc gtc act gtt att tcg gca gtt tgc aca c Gln Ser Leu Gln Gln Ala Val Thr Val Ile Ser Ala Val Cys Thr 8 850 855 860	cat 2592 His
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Met Ala Cys Leu Cys Leu Ala Asn Ile Ser Trp Ala Thr Val Cys Ala 1 10 15 15 aat agt act ggc gta gca gaa gat gaa cac tat gat ctc tca aat a Asn Ser Thr Gly Val Ala Glu Asp Glu His Tyr Asp Leu Ser Asn I	Ala atc 96 Ile gaa 144
Met Ala Cys Leu Cys Leu Ala Asn Ile Ser Trp Ala Thr Val Cys Ala 1 10 15 15 15 16 16 16 16 17 17 18 18 18 19 19 19 19 19 19 19 19 19 19 19 19 19	Ala atc 96 Ile gaa 144 Glu ctg 192

		-			aaa Lys		_				_					288
					gat Asp											336
					gga Gly											384
					tct Ser											432
ccc Pro 145	ttt Phe	att Ile	aac Asn	atg Met	gtg Val 150	gag Glu	atc Ile	ccc Pro	aga Arg	cag Gln 155	gtg Val	atg Met	ttt Phe	acc Thr	gtg Val 160	480
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					cgg Arg											576
					gaa Glu											624
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					gtc Val 230											720
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agt Ser	gga Gly	tgg Trp	gca Ala 20	gtt Val	gac Asp	cct Pro	tta Leu	gga Gly 25	acg Thr	att Ile	aat Asn	atc Ile	aat Asn 30	ttg Leu	cac His	96
			gtt Val													144
			gat Asp													192
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			tca Ser													288
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-118-

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cgc Arg	gac Asp 50	gaa Glu	agc Ser	cac His	tgt Cys	tat Tyr 55	cca Pro	tca Ser	ggc Gly	tgg Trp	cag Gln 60	gcc Ala	agg Arg	ctg Leu	ggg Gly		192
atg Met 65	att Ile	aac Asn	gaa Glu	ttt Phe	cat His 70	aaa Lys	caa Gln	ggt Gly	tca Ser	gct Ala 75	ttc Phe	tac Tyr	ttt Phe	ggc Gly	tta Leu 80		240
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tat Tyr 145	atg Met	ccg Pro	cac His	aat Asn	aaa Lys 150	cgc Arg	agc Ser	ggt Gly	gat Asp	tta Leu 155	ctg Leu	gcg Ala	cga Arg	ctg Leu	ggt Gly 160		480
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aat ctg agt ( Asn Leu Ser ( 50	gaa tcc gaa Glu Ser Glu	gtg cag gaa Val Gln Glu 55	cag ctg gat Gln Leu Asp 60	aat ctg gtc Asn Leu Val	aaa 192 Lys
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			ttt ggc gat Phe Gly Asp 90		
Ala Ala Glu			ttg tta ttg Leu Leu Leu		
			gcg cga atg Ala Arg Met		
gat atg gcg Asp Met Ala 130	gaa gtg gag Glu Val Glu	tcg acg ctg Ser Thr Leu 135	gaa caa ctg Glu Gln Leu 140	gca aat cgc Ala Asn Arg	gaa 432 .Glu
			cgc gaa ccg Arg Glu Pro 155		
-	-		gag gtt gaa Glu Val Glu 170		
Val Thr Asp			ggt gat tta Gly Asp Leu		

gaa gcc ctg gaa atc gaa gtg gca gaa ctg aaa cag cgt ctt gat tcg Glu Ala Leu Glu Ile Glu Val Ala Glu Leu Lys Gln Arg Leu Asp Ser 195 200 205	624
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gga gcc tgg tcg cct acg cgc gcg aaa gcc ctg cca att tgt gaa agc Gly Ala Trp Ser Pro Thr Arg Ala Lys Ala Leu Pro Ile Cys Glu Ser 35 40 45	144
tgg cgc att cct tat gcc gat tcg tta tcc agc ctt gcc gcc agt tgc Trp Arg Ile Pro Tyr Ala Asp Ser Leu Ser Ser Leu Ala Ala Ser Cys 50 55 60	192
gat gcg gtt ttt gtg cat tcc agc acc gcc agc cac ttt gac gtg gtc Asp Ala Val Phe Val His Ser Ser Thr Ala Ser His Phe Asp Val Val 65 70 75 80	210
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tac ggt gag tta aaa acg caa ctc gcc acc gca gcc tcg cta aga atg Tyr Gly Glu Leu Lys Thr Gln Leu Ala Thr Ala Ala Ser Leu Arg Met 130 135 140	432
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ggc Gly	gaa Glu	atg Met 195	ctg Leu	ttt Phe	gcc Ala	gag Glu	cac His 200	cat His	ttt Phe	tcg Ser	gct Ala	ggt Gly 205	cct Pro	ttg Leu	cag Gln	624
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cag Gln 225	gcc Ala	gtg Val	act Thr	gac Asp	ggt Gly 230	gcg Ala	ctc Leu	atc Ile	gac Asp	att Ile 235	acg Thr	gat Asp	atg Met	cgc Arg	gaa Glu 240	720
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ttc Phe	att Ile	gaa Glu 275	tgt Cys	gtg Val	caa Gln	aac Asn	cag Gln 280	aca Thr	gtt Val	ccg Pro	caa Gln	acc Thr 285	gcc Ala	ggc Gly	gaa Glu	864
cag Gln	gcc Ala 290	gtg Val	ctg Leu	gcg Ala	caa Gln	cgt Arg 295	atc Ile	gtt Val	gac Asp	aag Lys	atc Ile 300	tgg Trp	cgc Arg	gat Asp	gcg Ala	912
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ctg Lev	ttg Leu	act Thr	gtg Val	. Leu	ggc Gly	cto Leu	gat Asp	cgc Arg 25	Trp	atg Met	ago Ser	tgg Trp	aaa Lys 30	Thr	gcg Ala	96
cct	: tat	ato	tac	gac	gaa	ttg	cag	gat	cto	ccc	tac	: cgc	caç	gto	ggt	144

Pro	Tyr	Ile 35	Tyr	Asp	Glu	Leu	Gln 40	Asp	Leu	Pro	Tyr	Arg 45	Gln	Val	Gly	
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aat Asn	gag Glu	ccg Pro	atg Met 100	acc Thr	atg Met	cgc Arg	aaa Lys	gat Asp 105	tta Leu	atc Ile	gct Ala	gct Ala	ggt Gly 110	gtc Val	gac Asp	336
cca Pro	tca Ser	gat Asp 115	Ile	gtt Val	ctc Leu	gat Asp	tac Tyr 120	gca Ala	ggc Gly	ttt Phe	cgt Arg	acg Thr 125	ctg Leu	gat Asp	tcc Ser	384
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ctt Leu	tat Tyr	att Ile 195	Phe	aaa Lys	cgt Arg	gaa Glu	ccg Pro 200	Arg	ttt Phe	tta Leu	ggg	ccg Pro 205	Leu	gtc Val	cct Pro	624
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gto Val 225	Thr	ccc Pro	gaa Glu	cag Gln	tta Leu 230	Leu	gaa Glu	tta Leu	caa Gln	aag Lys 235	Lys	caa Gln	gga Gly	aag Lys	tag *	720
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	ttt Phe															96
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aaa Lys	aat Asn 50	ccc Pro	gga Gly	ctc Leu	ttt Phe	ttc Phe 55	gct Ala	tat Tyr	atg Met	gtg Val	gca Ala 60	tat Tyr	atc Ile	ggc Gly	ttc Phe	192
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gca Ala 465	ccg Pro	ctg Leu	gat Asp	cgg Arg	ggg Gly 470	cgc Arg	aaa Lys	gaa Glu	gtc Val	ctg Leu 475	aag Lys	cat His	gtg Val	cat His	cgc Arg 480	1440
ctg Leu	tgg Trp	gga Gly	ttt Phe	gat Asp 485	gtg Val	atg Met	ctc Leu	gaa Glu	cag Gln 490	caa Gln	aac Asn	gaa Glu	gac Asp	ggc Gly 495	agc Ser	1488
atc Ile	gag Glu	ttg Leu	ctg Leu 500	gaa Glu	cgt Arg	tgc Cys	ccg Pro	cca Pro 505	Arg	atg Met	gga Gly	aat Asn	ctg Leu 510	taa *		1533
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cga Arg	att Ile 130	aat Asn	att Ile	gat Asp	gaa Glu	gtt Val 135	tcg Ser	cca Pro	tca Ser	tta Leu	acg Thr 140	gtt Val	act Thr	gtg Val	gct Ala	432
aaa Lys 145	ttg Leu	gct Ala	tca Ser	gcc Ala	aga Arg 150	cat His	aac Asn	atg Met	ctt Leu	gaa Glu 155	cag Gln	tat Tyr	aaa Lys	att Ile	aat Asn 160	480
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ccg Pro	ctg Leu	tta Leu	atc Ile 180	aga Arg	acg Thr	gga Gly	tta Leu	cga Arg 185	gag Glu	atc Ile	aaa Lys	aag Lys	ttg Leu 190	agt Ser	ggt Gly	576
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				Thr	ctc Leu				Arg					Tyr	caa Gln	816

aaa ad Lys Tl	hr															864
aca ga Thr G	ag lu 90	aac Asn	ata Ile	ctg Leu	ttt Phe	ctt Leu 295	gcc Ala	agg Arg	gca Ala	gat Asp	aaa Lys 300	aac Asn	aat Asn	gtt Val	ttg Leu	912
gtg ad Val L 305	aa ys	ctg Leu	gac Asp	tcg Ser	ctt Leu 310	tct Ser	ctc Leu	aat Asn	aag Lys	gaa Glu 315	gtc Val	gaa Glu	aat Asn	ttg Leu	ttg Leu 320	960
gac to																1008
gag to																1056
tta to Leu So																1104
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gat a Asp I 385	tc le	gcc Ala	agc Ser	cct Pro	gga Gly 390	acg Thr	aaa Lys	att Ile	aat Asn	gag Glu 395	cct Pro	gaa Glu	aaa Lys	ctc Leu	ttc Phe 400	1200
cgt a Arg A	iga irg	ttt Phe	tgg Trp	cgg Arg 405	gga Gly	gat Asp	aat Asn	tcg Ser	cgt Arg 410	cat His	tcc Ser	gta Val	ggt Gly	cag Gln 415	gga Gly	1248
cta g Leu G	gc lly	ctt Leu	tct Ser 420	tta Leu	gtc Val	aaa Lys	gcg Ala	att Ile 425	gcc Ala	gaa Glu	ttg Leu	cat His	ggg Gly 430	gga Gly	agt Ser	1296
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ggc Gly	aga Arg 50	gat Asp	ggg Gly	ctt Leu	tat Tyr	ctt Leu 55	gcg Ala	ctg Leu	aag Lys	gat Asp	gat Asp 60	tat Tyr	gca Ala	ttg Leu	atc Ile	192
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acg Thr	tta Leu	aga Arg	aca Thr	gca Ala 85	aag Lys	caa Gln	acc Thr	cct Pro	gtt Val 90	att Ile	tgc Cys	ctt Leu	act Thr	gca Ala 95	agg Arg	288
gat Asp	tct Ser	gtc Val	gat Asp 100	gac Asp	aga Arg	gtc Val	aga Arg	ggg Gly 105	ctg Leu	gac Asp	agt Ser	ggg Gly	gca Ala 110	aat Asn	gat Asp	336
tat Tyr	ctg Leu	gta Val 115	aaa Lys	cct Pro	ttt Phe	tca Ser	ttt Phe 120	tct Ser	gag Glu	ttg Leu	ctg Leu	gca Ala 125	agg Arg	gtt Val	cgg Arg	384
gca Ala	caa Gln 130	tta Leu	agg Arg	caa Gln	cat His	cac His 135	gct Ala	ttg Leu	aat Asn	tca Ser	aca Thr 140	tta Leu	gaa Glu	atc Ile	agc Ser	432
ggc Gly 145	tta Leu	aga Arg	atg Met	gac Asp	tct Ser 150	gtt Val	agt Ser	cat His	agt Ser	gtg Val 155	agc Ser	agg Arg	gac Asp	aat Asn	atc Ile 160	480
agt Ser	att Ile	aca Thr	ctg Leu	acg Thr 165	cgc Arg	aag Lys	gag Glu	ttt Phe	cag Gln 170	tta Leu	ctt Leu	tgg Trp	cta Leu	ctg Leu 175	gcc Ala	528
tcc Ser	aga Arg	gct Ala	ggc Gly 180	gaa Glu	att Ile	ata Ile	ccc Pro	aga Arg 185	Thr	gtt Val	att Ile	gcg Ala	agt Ser 190	gaa Glu	att Ile	576
tgg Trp	gga Gly	atc Ile 195	Asn	ttt Phe	gat Asp	agt Ser	gat Asp 200	Thr	aat Asn	acg Thr	gtg Val	gac Asp 205	Val	gcc Ala	att Ile	624
cgc	agg Arg 210	Leu	cgc Arg	gca Ala	aaa Lys	gtt Val 215	Asp	gat Asp	cct Pro	ttt Phe	cct Pro 220	gaa Glu	aag Lys	cta Leu	att Ile	672
gcc Ala 225	Thr	atc Ile	cgg Arg	ggg	atg Met 230	Gly	tat Tyr	tca Ser	ttc Phe	gta Val 235	Ala	gta Val	aaa Lys	aaa Lys	taa *	720

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gct ttt agg gca tcc ttt cat tta cac ttt tta cga aat cat ggg Ala Phe Arg Ala Ser Phe His Leu His Phe Leu Arg Asn His Gly 20 25 30	g atc 96 / Ile
act aac aaa ata tcg ctt gtc agt tat att gta tgg cag gaa agg Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg 35 40 45	
gcg act gat att aca gat ccc caa agt gga gag ttt atg acc att Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile 50 . 55 60	
aat aag atg ttg ctg ggt gcg ctt ttg ctg gtt acc agt gcc gcc Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala 65 70 75	
gcc gca cca gcc acc gcg ggt tcg acc aat acc tcg gga att tct Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser 85 90	r Lys
tat gag tta agt agt ttc att gct gac ttt aag cat ttc aaa cca Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro 100 105 110	
gac acc gta cca gaa atg tac cgt acc gat gag tac aac att aag Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys 115 120 125	
tgg cag ttg cgt aac ctg ccc gcg cct gat gcc ggg acg cac tgg Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp 130 135 140	
tat atg ggt ggc gcg tac gtg ttg atc agc gac acc gac ggt aaz Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys 145 150 155	a atc 480 s Ile 160
att aaa gcc tac gac ggt gag att ttt tat cat cgc taa Ile Lys Ala Tyr Asp Gly Glu Ile Phe Tyr His Arg * 165 170	519

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cac His	tca Ser	aaa Lys 35	acg Thr	atg Met	atg Met	gcg Ala	gcg Ala 40	ttt Phe	atc Ile	atc Ile	gcc Ala	atc Ile 45	aaa Lys	ggc Gly	acc Thr	144
att Ile	aaa Lys 50	caa Gln	gcg Ala	gtg Val	atg Met	ctc Leu 55	gga Gly	ctg Leu	gca Ala	gca Ala	act Thr 60	att Ile	tcg Ser	cat His	acc Thr	192
gca Ala 65	gtg Val	gtc Val	tgg Trp	tta Leu	att Ile 70	gcc Ala	ttt Phe	ggc Gly	ggg	atg Met 75	gtg Val	atc Ile	agc Ser	aag Lys	cgc Arg 80	240
ttt Phe	act Thr	gct Ala	caa Gln	tca Ser 85	gca Ala	gaa Glu	ccg Pro	tgg Trp	ctc Leu 90	cag Gln	ctg Leu	att Ile	tcc Ser	gca Ala 95	gtg Val	288
atc Ile	att Ile	att Ile	agc Ser 100	acc Thr	gcg Ala	ttc Phe	tgg Trp	atg Met 105	Phe	tgg Trp	cgt Arg	acc Thr	tgg Trp 110	cgc Arg	ggc Gly	336
gaa Glu	cgc Arg	aac Asn 115	tgg Trp	ctg Leu	gag Glu	aat Asn	atg Met 120	cac His	ggg Gly	cat His	gat Asp	tat Tyr 125	gag Glu	cat His	cat His	384
cat His	cac His 130	Asp	cac His	gaa Glu	cat His	cac His 135	cac His	gac Asp	cat His	gga Gly	cat His 140	cat His	cac His	cat His	cac His	432
gaa Glu 145	His	ggc	gag Glu	tat Tyr	cag Gln 150	gat Asp	gcc Ala	cat His	gca Ala	cga Arg 155	gcc Ala	cat His	gcc Ala	aat Asn	gac Asp 160	480
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gtg Val	ctg Leu	ttg Leu 195	Ile	tgc Cys	att Ile	cag Gln	ttg Leu 200	Lys	gcc	ctg Leu	aca Thr	ctg Leu 205	Gly	gca Ala	aca Thr	624
ctg Leu	gtc Val 210	Val	agt Ser	ttc Phe	agc Ser	att Ile 215	Gly	ctg Leu	gcg Ala	tta Leu	acg Thr 220	Leu	gtc Val	acc	gta Val	672

ggc gtt ggc gca gca atc agc gtt cag cag gtc gca aaa cgc tgg agc Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser 235 230 235 240	720
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atc gcc ctg att tgt gaa ggt aac cct gcc gat cta ctg ggc cag tgg Ile Ala Leu Ile Cys Glu Gly Asn Pro Ala Asp Leu Leu Gly Gln Trp 35 40 45	144
gtg ctg gta cac gtc gga ttt gcc atg agc atc atc gac gaa gat gaa Val Leu Val His Val Gly Phe Ala Met Ser Ile Ile Asp Glu Asp Glu 50 55 60	192
gcc aaa gcc aca tta gac gca ctg cgc caa atg gat tac gac att acc Ala Lys Ala Thr Leu Asp Ala Leu Arg Gln Met Asp Tyr Asp Ile Thr 65 70 75 80	240
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-132-

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	55		60	
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gaa aaa att gg Glu Lys Ile Gl	ctg caa ctg Leu Gln Leu 85	ccg tat ggc a Pro Tyr Gly T 90	act atg acc ttt a Fhr Met Thr Phe T	cc gtt 288 hr Val 95.
	Gly Val Ser		tcc tgt tcg ctg a Ser Cys Ser Leu M 110	
			ggc caa cgc ctg a Gly Gln Arg Leu T 125	
gac tgc gca cga Asp Cys Ala Arc 130	atg atc ctt Met Ile Leu 135	Ser Leu Pro V	gtc acg aat ccg g Val Thr Asn Pro A 140	at gta 432 sp Val
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GIU	gtt Val	ccg Pro	gcg Ala	ttg Leu 85	ttt Phe	acc Thr	aac Asn	aaa Lys	atc Ile 90	tct Ser	ccg Pro	cat His	cag Gln	ctt Leu 95	ggc Gly	288
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, aag Lys	ctg Leu	acc Thr 115	ctg Leu	gtc Val	ggc Gly	gtg Val	atc Ile 120	ccg Pro	gaa Glu	tcg Ser	ctg Leu	gag Glu 125	cca Pro	cac His	atc Ile	384
ggc Gly	tta Leu 130	acg Thr	ccg Pro	acg Thr	gtt Val	gaa Glu 135	gca Ala	atg Met	att Ile	gaa Glu	cct Pro 140	gcg Ala	ctt Leu	gag Glu	cag Gln	432
gtt Val 145	ctg Leu	gct Ala	gcg Ala	ctg Leu	cgt Arg 150	gaa Glu	tct Ser	ggc Gly	gtg Val	gaa Glu 155	gcc Ala	atc Ile	cca Pro	cgg Arg	gag Glu 160	480
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ccg Pro 145	gaa Glu	gag Glu	ttc Phe	acc Thr	aaa Lys 150	gtt Val	cag Gln	aac Asn	aag Lys	atc Ile 155	aaa Lys	gat Asp	ctg Leu	gtt Val	gcc Ala 160	480
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gaa Glu	tac Tyr	ctg Leu	atc	aaa Lys 325	Gly	att Ile	cag Gln	gaa Glu	ago Ser 330	Ala	aag Lys	cac His	tcc Ser	tgg Trp 335	Tyr	1008

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act Thr	ttc Phe 370	tac Tyr	ggc Gly	aaa Lys	acg Thr	gta Val 375	gaa Glu	gtg Val	ggg Gly	cca Pro	ctg Leu 380	gct Ala	aat Asn	atg Met	ctg Leu	1152
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gat Asp	gac Asp	gtc Val 515	Gly	cct Pro	tac	gag Glu	cag Gln 520	Ser	ctg Leu	gtg Val	ggt Gly	aca Thr 525	Pro	gtt Val	gcc Ala	1584
gat Asp	ccg Pro 530	Asn	aaa Lys	ccg Pro	ctg Leu	gaa Glu 535	Val	gtg Val	cgt Arg	acc	Ile 540	His	tcc Ser	Phe	gac Asp	1632
ecq Pro 545	Cys	atg Met	gcc Ala	tgt Cys	gcg Ala 550	Val	cac His	gta Val	gtg Val	gat Asp 555	Ala	gac Asp	ggc Gly	aac Asn	gaa Glu 560	1680
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aag co Lys Ar	gt ctg rg Leu 35	gtg Val	ttc Phe	ggt Gly	ctg Leu	ggc Gly 40	tct Ser	gtc Val	tct Ser	gac Asp	ctg Leu 45	aac Asn	ggc Gly	ggc Gly	į	144
Phe Pr	eg tgg ro Trp 50	ggc Gly	gtg Val	tgg Trp	atc Ile 55	gcg Ala	ttt Phe	gac Asp	ctg Leu	ctg Leu 60	att Ile	ggc Gly	acc Thr	ggc Gly	1	192
ttt go Phe Al 65	cc tgt la Cys	ggc Gly	ggc Gly	tgg Trp 70	gcg Ala	ctg Leu	gcg Ala	tgg Trp	gcg Ala 75	gta Val	tac Tyr	gtc Val	ttt Phe	aac Asn 80	;	240
	gg caa ly Gln														;	288
ttt gg Phe Gl	gt tac ly Tyr	tca Ser 100	ctg Leu	ggt Gly	ggc Gly	ttg Leu	tcg Ser 105	atc Ile	act Thr	atc Ile	gac Asp	gtg Val 110	ggt Gly	cgc Arg	;	336
	gg aac rp Asn 115														;	384
Ser Va	ta ctg al Leu 30														•	432
	ca ctg la Leu														•	480
gtg to Val Se	cg cta er Leu	cag Gln	cga Arg 165	cta Leu	aac Asn	aag Lys	gtg Val	atg Met 170	ttc Phe	ttc Phe	atc Ile	atc Ile	gcg Ala 175	ctc Leu		528
	cg ctg la Leu														:	576
atc to	cg gcg	ggc	tac	aag	gtg	cat	ccg	ttg	tgg	cag	agc	tat	gaa	atg	1	624

Ile	Ser	Ala 195	Gly	Tyr	Lys	Val	His 200	Pro	Leu	Trp	Gln	Ser 205	Tyr	Glu	Met	
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gtc Val 225	atc Ile	ttt Phe	gaa Glu	ggt Gly	tcg Ser 230	ctg Leu	gtg Val	cag Gln	gcg Ala	ggt Gly 235	ctg Leu	cgt Arg	ggc Gly	aac Asn	ggt Gly 240	720
ccg Pro	gat Asp	gaa Glu	aag Lys	agt Ser 245	ctg Leu	ttt Phe	gtt Val	aag Lys	ctg Leu 250	acc Thr	aac Asn	acc Thr	atc Ile	agt Ser 255	gtg Val	768
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ctc Leu	att Ile 370	Arg	cta Leu	ctg Leu	ccg Pro	ata Ile 375	ctt Leu	cct Pro	cct Pro	tta Leu	aaa Lys 380	caa Gln	aac Asn	gat Asp	cat His	1152
	Arg				agc Ser 390						•					1179
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	1> C	DS 1)	. (98	7)												

	)> 20															
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cca Pro	att Ile	ccg Pro 35	gga Gly	tcg Ser	ctg Leu	ggg Gly	atg Met 40	ttg Leu	tac Tyr	gac Asp	tcg Ser	acc Thr 45	ttg Leu	tgc Cys	gta Val	144
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gaa Glu	tac Tyr	cac His	tat Tyr	ccg Pro	cgt Arg	cag Gln	acg Thr	ctg Leu	aaa Lys	tct Ser	ggc	gac	act Thr	tac Tyr	ctg Leu	720

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gcg ggc tta acc gtg Ala Gly Leu Thr Val 305	ctg gtt cgt cgc aac Leu Val Arg Arg Asn 310	acc aaa aac gac cat Thr Lys Asn Asp His 315	cac 960 His 320
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atg cta caa tgt ggc Met Leu Gln Cys Gly 1 5  tcg tcg ttg ccc gtt Ser Ser Leu Pro Val 20  gat tgt gcg ccg cag Asp Cys Ala Pro Gln 35  tca acc tgg ctg ccg Ser Thr Trp Leu Pro 50  aaa att atc ctg ctg	Ala Lys Asn Val Asn 10 gct gcc gtc tta cct Ala Ala Val Leu Pro 25 gta tta tta agt gcg Val Leu Leu Ser Ala 40 ctg caa ctg ctg gcg Leu Gln Leu Leu Ala	Pro Leu Glu Arg Phe 15 gaa tta ctt acc gct Glu Leu Leu Thr Ala 30 ccg acc ggg gcc ggg Pro Thr Gly Ala Gly 45 cat ccc ggc att aac His Pro Gly Ile Asn 60 gcg gcg cgt aac gtc	Ctc 96 Leu 96 Leu 144 Lys 192 Gly 192 Gcg 240

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aaa Lys	gaa Glu	caa Gln 355	gca Ala	gaa Glu	cgc Arg	gcc Ala	gcg Ala 360	gcg Ala	caa Gln	agt Ser	gaa Glu	ccg Pro 365	gag Glu	atc Ile	tta Leu	1104
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gaa Glu 545	Trp	ttg Leu	atc Ile	gca Ala	ccg Pro 550	Leu	tta Leu	ttg Leu	cag Gln	ggc Gly 555	Ser	gcc Ala	tcg Ser	ccg Pro	gat Asp 560	1680
gcg Ala	cgg	att Ile	tta Leu	ctg Leu 565	Ala	ctg Leu	ctg Lev	gtc Val	gat Asp 570	Ile	gat Asp	gag Glu	tta Leu	gta Val 575	caa Gln	1728

								tct Ser 585								1776
gcg Ala	caa Gln	ggt Gly 595	acg Thr	ctg Leu	aaa Lys	gcc Ala	tgg Trp 600	cgt Arg	cgg Arg	cta Leu	caa Gln	atc Ile 605	ggt Gly	cag Gln	ttg Leu	1824
acg Thr	gtg Val 610	aaa Lys	gtg Val	cag Gln	ccg Pro	ctg Leu 615	gcg Ala	aaa Lys	ccg Pro	tca Ser	gaa Glu 620	gac Asp	gag Glu	ttg Leu	cat His	1872
								gat Asp								1920
tgg Trp	acg Thr	gcg Ala	gaa Glu	gcg Ala 645	gaa Glu	cag Gln	cta Leu	cgc Arg	ttg Leu 650	cgt Arg	ttg Leu	tta Leu	tgc Cys	gcc Ala 655	gca Ala	1968
aag Lys	tgg Trp	ttg Leu	ccg Pro 660	gaa Glu	tat Tyr	gac Asp	tgg Trp	cca Pro 665	gcg Ala	gtt Val	gat Asp	gat Asp	gaa Glu 670	agt Ser	tta Leu	2016
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tca Ser	cta Leu 690	cgc Arg	ggc Gly	ctg Leu	aaa Lys	tca Ser 695	ctc Leu	gac Asp	att Ile	tat Tyr	cag Gln 700	gca Ala	cta Leu	cgc Arg	gga Gly	2112
tta Leu 705	ctt Leu	gat Asp	tgg Trp	gga Gly	atg Met 710	cag Gln	caa Gln	cgt Arg	ctg Leu	gat Asp 715	agt Ser	gaa Glu	ttg Leu	cct Pro	gcg Ala 720	2160
cat His	tac Tyr	act Thr	gtg Val	ccg Pro 725	acg Thr	gga Gly	agc Ser	cgg Arg	atc Ile 730	gcc Ala	att Ile	cgt Arg	tat Tyr	cat His 735	gaa Glu	2208
gat Asp	aac Asn	ccg Pro	ccc Pro 740	gcg Ala	ctg Leu	gcg Ala	gtg Val	aga Arg 745	atg Met	caa Gln	gag Glu	atg Met	ttt Phe 750	ggc Gly	gag Glu	2256
gcc Ala	acc Thr	aat Asn 755	ccg Pro	acg Thr	atc Ile	gcc Ala	cag Gln 760	Gly	cgc Arg	gtg Val	ccg Pro	ctg Leu 765	gtg Val	ctg Leu	gag Glu	2304
								tta Leu								2352
gac Asp 785	ttc Phe	tgg Trp	aaa Lys	gga Gly	gcg Ala 790	tac Tyr	cgt Arg	gag Glu	gtg Val	caa Gln 795	aaa Lys	gag Glu	atg Met	aaa Lys	800 GTA GGG	2400
cgt Arg	tat Tyr	ccc Pro	aaa Lys	cat His 805	gtc Val	tgg Trp	ccg Pro	gac Asp	gac Asp 810	ccg Pro	gca Ala	aat Asn	act Thr	gca Ala 815	ccg Pro	2448

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Val Ser Gly T	ca tct ttg hr Ser Leu 20	atc tcc tct Ile Ser Ser 25	ctg tat ggt gat Leu Tyr Gly Asp	tcg ctt tcc Ser Leu Ser 30	96
cat cgt ggt g His Arg Gly G 35	gt gaa atc ly Glu Ile	tgg ttg ggt Trp Leu Gly 40	agt ctg gct gct Ser Leu Ala Ala 45	ttg ctg gaa Leu Leu Glu	144
ggg ctg gga t Gly Leu Gly P 50	tt ggt gag he Gly Glu	cgt ttc gtg Arg Phe Val 55	cgc acc gct ttg Arg Thr Ala Leu 60	ttt cgt ctt Phe Arg Leu	192
aat aaa gaa g Asn Lys Glu G 65	gc tgg ctg ly Trp Leu 70	gat gtt tcc Asp Val Ser	cgc atc ggg cga Arg Ile Gly Arg 75	cgc agt ttc Arg Ser Phe 80	240
tat agc ctc a Tyr Ser Leu S	gt gat aaa er Asp Lys 85	ggc ttg cgc Gly Leu Arg	ctg acg cga cgg Leu Thr Arg Arg 90	gca gaa agt Ala Glu Ser 95	288
Lys Ile Tyr A	gc gca gag rg Ala Glu 00	caa cct gca Gln Pro Ala 105	tgg gat ggt aaa Trp Asp Gly Lys	tgg ctc ctg Trp Leu Leu 110	336
ttg ctc tcg g Leu Leu Ser G 115	gaa ggt tta Gly Leu	gat aaa tca Asp Lys Ser 120	acg ctg gct gat Thr Leu Ala Asp 125	gtc aaa aag Val Lys Lys	384
cag ttg atc t Gln Leu Ile T 130	gg caa ggt Trp Gln Gly	ttt ggc gca Phe Gly Ala 135	ctg gca ccc agc Leu Ala Pro Ser 140	ctg atg gca Leu Met Ala	432
tcg ccg tcg c Ser Pro Ser G 145	caa aaa ctg Gln Lys Leu 150	gcc gat gta Ala Asp Val	cag aca ctt ttg Gln Thr Leu Leu 155	cat gaa gcg His Glu Ala 160	480
ggt gtg gcg g Gly Val Ala A	gat aac gtg Asp Asn Val 165	att tgt ttt Ile Cys Phe	gaa gcg caa ata Glu Ala Gln Ile 170	cca ctg gcg Pro Leu Ala 175	528

ctt tct cgc gca gca ctg cgt gcc aga gta gaa gag tgc tgg cat tta Leu Ser Arg Ala Ala Leu Arg Ala Arg Val Glu Glu Cys Trp His Leu 180 185 190	576
act gaa caa aat gcc atg tac gaa acc ttt att cag tca ttc cgc ccg Thr Glu Gln Asn Ala Met Tyr Glu Thr Phe Ile Gln Ser Phe Arg Pro 195 200 205	624
ctg gtg ccg ctt tta aaa gag gcg gca gac gag tta acc ccg gag cgg Leu Val Pro Leu Leu Lys Glu Ala Ala Asp Glu Leu Thr Pro Glu Arg 210 215 220	672
gca ttt cat att cag ctt tta ctg atc cat ttt tat cgc cgt gtc gtc Ala Phe His Ile Gln Leu Leu Ile His Phe Tyr Arg Arg Val Val 225 230 235 240	720
ctt aaa gac cca ttg ttg ccg gag gag ttg ctt ccg gca cac tgg gca Leu Lys Asp Pro Leu Leu Pro Glu Glu Leu Leu Pro Ala His Trp Ala 245 250 255	768
ggg cat acg gcg cgt cag ctg tgt atc aac att tat cag cgc gta gcg Gly His Thr Ala Arg Gln Leu Cys Ile Asn Ile Tyr Gln Arg Val Ala 260 265 270	816
cct gct gct tta gcg ttc gtt agt gaa aaa ggt gaa acc tcg gtc ggt Pro Ala Ala Leu Ala Phe Val Ser Glu Lys Gly Glu Thr Ser Val Gly 275 280 285	864
gaa ctg cct gcg ccg gga agc ctg tat ttt caa cgt ttt ggc ggc ttg Glu Leu Pro Ala Pro Gly Ser Leu Tyr Phe Gln Arg Phe Gly Gly Leu 290 295 300	912
aat att gaa cag gag gcg tta tgc caa ttt atc aga tag Asn Ile Glu Gln Glu Ala Leu Cys Gln Phe Ile Arg * 305 310 315	951
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aag ggc gtt tac gtt ggg cca aat gcc agc ctg cgt ggc gat ttt ggt Lys Gly Val Tyr Val Gly Pro Asn Ala Ser Leu Arg Gly Asp Phe Gly 35 40 45	144
cgt atc gtg gtg aaa gat ggc gcg aac att cag gat aat tgc gtt atg	192

Arg	Ile 50	Val	Val	Lys	Asp	Gly 55	Ala	Asn	Ile	Gln	Asp 60	Asn	Cys	Val	Met	
cac His 65	ggt Gly	ttt Phe	ccc Pro	gag Glu	cag Gln 70	gat Asp	act Thr	gtt Val	gta Val	gga Gly 75	gaa Glu	gat Asp	gga Gly	cat His	att Ile 80	240
ggt Gly	cat His	agc Ser	gct Ala	atc Ile 85	ctt Leu	cac His	ggc Gly	tgc Cys	att Ile 90	atc Ile	cgc Arg	cgc Arg	aat Asn	gca Ala 95	tta Leu	288
gtg Val	gga Gly	atg Met	aac Asn 100	gcg Ala	gta Val	gtg Val	atg Met	gac Asp 105	ggt Gly	gcg Ala	gtg Val	att Ile	ggc Gly 110	gag Glu	aac Asn	336
agc Ser	att Ile	gtt Val 115	ggt Gly	gca Ala	tcc Ser	gca Ala	ttt Phe 120	gtg Val	aaa Lys	gcc Ala	aaa Lys	gca Ala 125	gaa Glu	atg Met	cca Pro	384
gct Ala	aat Asn 130	tac Tyr	ctg Leu	att Ile	gtc Val	ggc Gly 135	agc Ser	ccg Pro	gcg Ala	aaa Lys	gcg Ala 140	att Ile	cgt Arg	gaa Glu	ctc Leu	432
agt Ser 145	gag Glu	cag Gln	gag Glu	ttg Leu	gca Ala 150	tgg Trp	aaa Lys	aag Lys	cag Gln	ggt Gly 155	acg Thr	cat His	gag Glu	tac Tyr	cag Gln 160	480
gtg Val	ctg Leu	gtg Val	aca Thr	cgc Arg 165	tgt Cys	aag Lys	cag Gln	acg Thr	tta Leu 170	cat His	caa Gln	gtc Val	gag Glu	cca Pro 175	ttg Leu	528
cgg Arg	gaa Glu	att Ile	gaa Glu 180	cct Pro	ggc Gly	agg Arg	aaa Lys	cgc Arg 185	ctg Leu	gta Val	ttt Phe	gat Asp	gag Glu 190	aat Asn	ctg Leu	576
_	_	aaa Lys 195														591
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aat Asn	gga Gly	att Ile	tat Tyr 20	Ala	gtt Val	tgt Cys	tcc Ser	gca Ala 25	His	ccg Pro	ctg Leu	gtg Val	ctg Leu 30	Glu	gct Ala	96
gca Ala	ato	cgc Arg	tac Tyr	gcc	agt Ser	gca Ala	aac Asn	caa Gln	acq Thr	ccg	tta Leu	ctg Leu	att Ile	gaa Glu	gca Ala	144

35 40 192 acc tcc aat cag gta gac cag ttc ggc ggt tat acc gga atg acg ccc Thr Ser Asn Gln Val Asp Gln Phe Gly Gly Tyr Thr Gly Met Thr Pro gcc gat ttt cgc ggc ttt gtt tgt cag ctc gcc gac tcg ttg aat ttc 240 Ala Asp Phe Arg Gly Phe Val Cys Gln Leu Ala Asp Ser Leu Asn Phe 288 ccg cag gat gcg ttg att ctg ggt ggt gac cat ctg ggg cca aac cgc Pro Gln Asp Ala Leu Ile Leu Gly Gly Asp His Leu Gly Pro Asn Arg tgg caa aac ctg ccg gcc gct cag gca atg gcc aat gcc gat gat ttg 336 Trp Gln Asn Leu Pro Ala Ala Gln Ala Met Ala Asn Ala Asp Asp Leu 100 105 att aaa agc tac gtt gcg gca gga ttc aaa aaa atc cac ctt gat tgc 384 Ile Lys Ser Tyr Val Ala Ala Gly Phe Lys Lys Ile His Leu Asp Cys 120 432 age atg tee tgt cag gae gat ceg att eee tta act gat gae ate gtg Ser Met Ser Cys Gln Asp Asp Pro Ile Pro Leu Thr Asp Asp Ile Val 135 480 get gaa ege gee egt etg geg aaa gtg geg gaa gaa ace tgt ett Ala Glu Arg Ala Ala Arg Leu Ala Lys Val Ala Glu Glu Thr Cys Leu 150 155 gaa cac ttt ggc gaa gcc gat ctg gag tat gtc att ggt acc gaa gtg 528 Glu His Phe Gly Glu Ala Asp Leu Glu Tyr Val Ile Gly Thr Glu Val 165 ccg gta cct ggc gcg cat gaa acc tta agc gag ctg gcg qtc acc 576 Pro Val Pro Gly Gly Ala His Glu Thr Leu Ser Glu Leu Ala Val Thr 185 acg ccg gat gcc gcc cgc gcc acg ctg gaa gcc cat cgt cac gcc ttt 624 Thr Pro Asp Ala Ala Arg Ala Thr Leu Glu Ala His Arg His Ala Phe 195 qaa aag caa ggt ttg aat gcc atc tgg cca cgc atc att gcc ctg gtg 672 Glu Lys Gln Gly Leu Asn Ala Ile Trp Pro Arg Ile Ile Ala Leu Val 215 210 gtt caa ccc ggc gtc gaa ttc gat cac acc aac gtt att gat tat cag 720 Val Gln Pro Gly Val Glu Phe Asp His Thr Asn Val Ile Asp Tyr Gln 225 240 768 ccc gcc aaa gcg agc gcc tta agc cag atg gtc gaa aac tac gaa acg Pro Ala Lys Ala Ser Ala Leu Ser Gln Met Val Glu Asn Tyr Glu Thr 245 816 ctg att ttc gaa gcg cac tct acc gat tat caa acg ccg caa tcg ctg Leu Ile Phe Glu Ala His Ser Thr Asp Tyr Gln Thr Pro Gln Ser Leu 270 260 864 cgc cag ctg gtg att gac cac ttt gcc att ctg aaa gtt ggc cca gcg Arg Gln Leu Val Ile Asp His Phe Ala Ile Leu Lys Val Gly Pro Ala

275		280	285		
ctg acc ttc gcc Leu Thr Phe Ala 290	ctg cgt gaa Leu Arg Glu 295	gct ctg ttc Ala Leu Phe	tct ctg gcg gc Ser Leu Ala Al 300	eg att gaa 91 la Ile Glu	12
gaa gaa ctg gtg Glu Glu Leu Val 305	cca gcg aaa Pro Ala Lys 310	gcc tgt tct Ala Cys Ser	ggt ctg cgt ca Gly Leu Arg G 315	ag gtg ctg 90 ln Val Leu 320	60
gaa gac gtg atg Glu Asp Val Met	ctc gac cgc Leu Asp Arg 325	ccg gaa tac Pro Glu Tyr 330	tgg caa agc ca Trp Gln Ser H	ac tac cac 100 is Tyr His 335	80
ggt gac ggc aac Gly Asp Gly Asn 340	Ala Arg Arg	ctg gcg cgt Leu Ala Arg 345	Gly Tyr Ser T	ac tcg gat 109 yr Ser Asp 50	56
cgc gtg cgc tat Arg Val Arg Tyr 355	tac tgg ccg Tyr Trp Pro	gac agc cag Asp Ser Gln 360	att gat gac g Ile Asp Asp A 365	ct ttc gct 110 la Phe Ala	04 .
cat ctg gta cgt His Leu Val Arg 370	aat ctg gcg Asn Leu Ala 375	gat tca cca Asp Ser Pro	att ccg ctg c Ile Pro Leu P 380	cg ctg atc .11 ro Leu Ile	52
agc cag tat ctg Ser Gln Tyr Leu 385	ccg ctg cag Pro Leu Gln 390	tac gtg aaa Tyr Val Lys	gtt cgc tcc g Val Arg Ser G 395	gc gag ctg 12 ly Glu Leu 400	00
cag cca acg cca Gln Pro Thr Pro	cgg gaa ctc Arg Glu Leu 405	att atc aac Ile Ile Asn 410	cat att cag g His Ile Gln A	ac atc ctg 12 sp Ile Leu 415	48
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caa tgg gtc gga Gln Trp Val Gly 35	a ttt gcg ggg / Phe Ala Gly	gca aat ctg Ala Asn Leu 40	gtg ctg gta g Val Leu Val A 45	cc aac gat 1 la Asn Asp	.44

			ctg atg gaa atg gta Leu Met Glu Met Val 60	
			ctg caa aaa gtt atc Leu Gln Lys Val Ile 75	
-			atc ctg ctg gtt tgt Ile Leu Leu Val Cys 95	
			ggt ggc gtt ccg gtg Gly Gly Val Pro Val 110	
			aat ggc aaa caa caa Asn Gly Lys Gln Gln 125	
			atc gca gca ttt aac Ile Ala Ala Phe Asn 140	
			cag ggc gtc ccg aca Gln Gly Val Pro Thr 155	
cct gct gtg gac Pro Ala Val Asp		-		510 (
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			acc cat atg cac cgc Thr His Met His Arg 30	
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			gtg tgg atg ggg ctg Val Trp Met Gly Leu 60	

Pro Leu Ala	ggc	gca Ala	cag Gln 70	ccg Pro	cct Pro	aac Asn	gtg Val	att Ile 75	atc Ile	ggt Gly	act Thr	atc Ile	gtc Val 80	240
ggc acg gcc Gly Thr Ala	ttt Phe	gcc Ala 85	att Ile	act Thr	act Thr	ggc Gly	gtg Val 90	aaa Lys	ccc Pro	gat Asp	gtc Val	gca Ala 95	gta Val	288
ggt gtc gcc Gly Val Ala	gta Val 100	cct Pro	ttc Phe	gct Ala	gtc Val	gca Ala 105	gta Val	cag Gln	atg Met	ggg Gly	att Ile 110	acc Thr	ttc Phe	336
ctg ttc tcc Leu Phe Ser 11	Val	atg Met	tcc Ser	ggc Gly	gtg Val 120	atg Met	tct Ser	cgc Arg	tgc Cys	gac Asp 125	ctg Leu	gca Ala	aca Thr	384
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gtg cat tg Met His Cy	Tyr	Asn 5 gga	Gly	Met acg	Thr	Gly aag	Leu 10 cgc	His	His tgg	Arg ctg	Glu gaa	Pro 15 ctg	Gly ata	48 96
gtg cat tg Met His Cy 1	g Tyr c gcg y Ala 20 t cat y His	Asn 5 gga Gly cat	Gly tta Leu gtg	Met acg Thr	Thr gac Asp	aag Lys 25	Leu 10 cgc Arg	His gcc Ala atg	His tgg Trp	Arg ctg Leu ctg	gaa Glu 30 tgt	Pro 15 ctg Leu	Gly ata Ile	
gtg cat tg Met His Cy 1 atg gtt gg Met Val Gl gcc gat gg Ala Asp Gl	g Tyr g g g g g Ala 20 t cat y His	Asn 5 gga Gly cat His	Gly tta Leu gtg Val	Met acg Thr cat His	gac Asp ccg Pro 40	aag Lys 25 gcg Ala	Leu 10 cgc Arg gca Ala	His gcc Ala atg Met	tgg Trp tcg Ser	ctg Leu ctg Leu 45	gaa Glu 30 tgt Cys	Pro 15 ctg Leu tgt Cys	ata Ile tgc Cys	96
gtg cat tg Met His Cy 1 atg gtt gg Met Val Gl gcc gat gg Ala Asp Gl 3 tgt gcg aa Cys Ala Ly	gcg y Ala 20 t cat y His a gag s Glu	Asn 5 gga Gly cat His aga Arg	Gly tta Leu gtg Val atc Ile	Met acg Thr cat His gta Val 55	gac Asp ccg Pro 40 ctg Leu acg	aag Lys 25 gcg Ala atc	Leu 10 cgc Arg gca Ala acc Thr	His gcc Ala atg Met gac Asp	tgg Trp tcg Ser gcg Ala 60	ctg Leu ctg Leu 45 atg Met	gaa Glu 30 tgt Cys cag Gln	Pro 15 ctg Leu tgt Cys gca Ala	ata Ile tgc Cys gct Ala	96 144
gtg cat tg Met His Cy 1 atg gtt gg Met Val Gl gcc gat gg Ala Asp Gl 3 tgt gcg aa Cys Ala Ly 50 ggg atg cc Gly Met Pr	gcg y Ala 20 t cat y His a gag s Glu g gat o Asp	Asn 5 gga Gly cat His aga Arg	Gly tta Leu gtg Val atc Ile cgc Arg 70	Met acg Thr cat His gta Val 55 tat Tyr acc	Thr  gac Asp  ccg Pro 40  ctg Leu  acg Thr	aag Lys 25 gcg Ala atc Ile tta Leu	Leu 10 cgc Arg gca Ala acc Thr tgt Cys	gcc Ala atg Met gac Asp ggt Gly 75	tgg Trp tcg Ser gcg Ala 60 gaa Glu	ctg Leu ctg Leu 45 atg Met gaa Glu	gaa Glu 30 tgt Cys cag Gln gtg Val	Pro 15 ctg Leu tgt Cys gca Ala cag Gln	ata Ile tgc Cys gct Ala atg Met. 80	96 144 192
gtg cat tg Met His Cy  1  atg gtt gg Met Val Gl  gcc gat gg Ala Asp Gl 3  tgt gcg aa Cys Ala Ly 50  ggg atg cc Gly Met Pr 65  cac ggt gg	g gcg y Ala 20 cat y His Glu gat o Asp c gtt y Val	Asn 5 gga Gly cat His aga Arg ggt Gly gtc Val 85	Gly tta Leu gtg Val atc Ile cgc Arg 70 cgt Arg	Met acg Thr cat His gta Val 55 tat Tyr acc Thr	Thr  gac Asp  ccg Pro 40  ctg Leu  acg Thr  gcg Ala	aag Lys 25 gcg Ala atc Ile tta Leu tct Ser	Leu 10 cgc Arg gca Ala acc Thr tgt Cys ggt Gly 90 atg	gcc Ala atg Met gac Asp ggt Gly 75	tgg Trp tcg Ser gcg Ala 60 gaa Glu ctg Leu	ctg Leu ctg Leu 45 atg Met gaa Glu gcg Ala	gaa Glu 30 tgt Cys cag Gln gtg Val ggc Gly	tgt Cys gca Ala cag Gln agt Ser 95	ata Ile tgc Cys gct Ala atg Met. 80 acg Thr	96 144 192 240

Thr Pro Ala Glu 115	Ala Ile His	Met Ala Ser 120	Leu His Pro Ala 125	Arg Met
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aga gtc gtt gcg Arg Val Val Ala 145	ctg gat agc Leu Asp Ser 150	ggg cta cat Gly Leu His	gtg caa caa atc Val Gln Gln Ile 155	t tgg att 480 Trp Ile 160
cag ggt caa tta Gln Gly Gln Leu	gct tcg ttt Ala Ser Phe 165	tga *		504
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gca ttt atc ggt Ala Phe Ile Gly 65				
aaa aac ttc agc Lys Asn Phe Ser				
gac tac ctg aac Asp Tyr Leu Asn 100				e Gly Arg
tcc ggc aac agc Ser Gly Asn Ser 115				
ttt gta ccg gaa Phe Val Pro Glu				

	130					135					140					
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atg Met	ccc Pro	gca Ala	gaa Glu	acg Thr 165	cac His	gat Asp	cgc Arg	ggc Gly	ttt Phe 170	gcg Ala	atg Met	acc Thr	agc Ser	agc Ser 175	att Ile	528
acc Thr	acc Thr	atg Met	atg Met 180	gcc Ala	agc Ser	tgc Cys	ctc Leu	gcg Ala 185	gtt Val	ttc Phe	gca Ala	cct Pro	gag Glu 190	acg Thr	atc Ile	576
aac Asn	agc Ser	caa Gln 195	acc Thr	ttc Phe	cgc Arg	gac Asp	gtg Val 200	gcg Ala	gat Asp	cgt Arg	tgc Cys	cag Gln 205	gcg Ala	atc Ile	ctg Leu	624
acc Thr	tca Ser 210	ctg Leu	ggc Gly	gat Asp	ttc Phe	agc Ser 215	gaa Glu	ggt Gly	gtg Val	ttt Phe	ggt Gly 220	tac Tyr	gca Ala	ccg Pro	tgg Trp	672
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gag Glu	tcg Ser	gcg Ala	ctg Leu	aaa Lys 245	gtg Val	ctg Leu	gaa Glu	ctg Leu	acg Thr 250	gcg Ala	ggt Gly	aaa Lys	ctg Leu	gcg Ala 255	gcc Ala	768
ttt Phe	tat Tyr	gat Asp	tct Ser 260	cca Pro	acc Thr	gga Gly	ttc Phe	cgt Arg 265	cat Kis	gga Gly	cca Pro	aaa Lys	tcg Ser 270	ctg Leu	gtc Val	816
gat Asp	gac Asp	gaa Glu 275	acg Thr	ctg Leu	gtg Val	gtg Val	gta Val 280	ttt Phe	gtc Val	tcc Ser	agc Ser	cac His 285	cct Pro	tac Tyr	acc Thr	864
cgt Arg	cag Gln 290	tat Tyr	gat Asp	ctt Leu	gat Asp	ctg Leu 295	ctg Leu	gct Ala	gaa Glu	ctt Leu	cgc Arg 300	cgt Arg	gac Asp	aac Asn	cag Gln	912
gca Ala 305	atg Met	cgt Arg	gta Val	atc Ile	gcc Ala 310	atc Ile	gcc Ala	gcg Ala	gaa Glu	agc Ser 315	agc Ser	gac Asp	atc Ile	gtc Val	gct Ala 320	960
gcc Ala	ggt Gly	cca Pro	cat His	atc Ile 325	atc Ile	ctg Leu	cca Pro	ccg Pro	tca Ser 330	cgt Arg	cac His	ttt Phe	atc Ile	gac Asp 335	gtt Val	1008
gag Glu	cag Gln	gca Ala	ttt Phe 340	tgc Cys	ttc Phe	ctg Leu	atg Met	tac Tyr 345	gcc Ala	cag Gln	acg Thr	ttt Phe	gca Ala 350	ctg Leu	atg Met	1056
cag Gln	tcg Ser	ctg Leu 355	cac His	atg Met	ggc Gly	aat Asn	acg Thr 360	ccg Pro	gat Asp	acc Thr	cca Pro	tca Ser 365	gcc Ala	agt Ser	ggc	1104
acc Thr	gtt Val	aac Asn	cgc Arg	gtg Val	gtg Val	caa Gln	ggc Gly	gta Val	atc Ile	att Ile	cat His	ccg Pro	tgg Trp	cag Gln	gca Ala	1152

1155

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-	cac ggc His Gly 180	tta tac Leu Tyr	agc aaa Ser Lys 185	acg ccg Thr Pro	aag att Lys Ile	gat tto Asp Phe 190	cag Gln	576
cgg ctg gcg Arg Leu Ala 195	gaa att Glu Ile	cgt gaa Arg Glu	gtg gtg Val Val 200	gat gtt Asp Val	cct ctg Pro Leu 205	gtg ctg Val Leu	cat His	624
ggt gcc agc Gly Ala Ser 210	gat gtt Asp Val	ccg gat Pro Asp 215	gaa ttt Glu Phe	gtc cgt Val Arg	cgc act Arg Thr 220	att gaa Ile Glu	ctt Leu	672
ggc gtc aca Gly Val Thr 225	Lys Val	aac gtt Asn Val 230	gcc aca Ala Thr	gaa tta Glu Leu 235	aaa ata Lys Ile	gcc ttc Ala Phe	gct Ala 240	720
ggc gcg gtt Gly Ala Val	aaa gcc Lys Ala 245	tgg ttt Trp Phe	gcg gaa Ala Glu	aat ccg Asn Pro 250	cag ggt Gln Gly	aat gat Asn Asp 255	Pro	768
cgt tat tat Arg Tyr Tyr	atg cgc Met Arg 260	gtc gga Val Gly	atg gat Met Asp 265	gcg atg Ala Met	aaa gaa Lys Glu	gtt gtc Val Val 270	aga Arg	816
aat aaa att Asn Lys Ile 275								861
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<213> Esche:	richia co	li			ì			
		li						
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atg gat ctt ggt tgc tat cgc ggt ttg cgt cat cgt cgt ggt ct Met Asp Leu Gly Cys Tyr Arg Gly Leu Arg His Arg Arg Gly Le 85 90 9	u Pro
gtt cgc ggt cag cgt acc aag acc aac gca cgt acc cgt aag gg Val Arg Gly Gln Arg Thr Lys Thr Asn Ala Arg Thr Arg Lys Gl 100 105 110	
cgc aaa ccg atc aag aaa taa Arg Lys Pro Ile Lys Lys * 115	357
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tct gac ggc gtg gct cat atc cat gct tct ttc aac aac acc at Ser Asp Gly Val Ala His Ile His Ala Ser Phe Asn Asn Thr Il 20 25 30	c gtg 96 e Val
act atc act gat cgt cag ggt aac gcg ttg ggt tgg gca aca gc Thr Ile Thr Asp Arg Gln Gly Asn Ala Leu Gly Trp Ala Thr Al 35 40 45	
ggt tcc ggt ttc cgt ggt tct cgc aaa tcc act ccg ttt gca gc Gly Ser Gly Phe Arg Gly Ser Arg Lys Ser Thr Pro Phe Ala Al 50 55 60	
gtt gca gca gag cgt tgc gct gac gcc gtg aaa gaa tac ggc at Val Ala Ala Glu Arg Cys Ala Asp Ala Val Lys Glu Tyr Gly Il 65 70 75	
aat ctg gaa gtt atg gtt aaa ggt ccg ggt cca ggc cgc gaa tc Asn Leu Glu Val Met Val Lys Gly Pro Gly Pro Gly Arg Glu Se 85 90 9	t act 288 or Thr
att cgt gct ctg aac gcc gca ggt ttc cgc atc act aac att ac Ile Arg Ala Leu Asn Ala Ala Gly Phe Arg Ile Thr Asn Ile Th 100 105 110	t gat 336 r Asp
gtg act ccg atc cct cat aac ggt tgt cgt ccg ccg aaa aaa cg Val Thr Pro Ile Pro His Asn Gly Cys Arg Pro Pro Lys Lys Ar 115 120 125	
gta taa Val *	390

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195 200 205

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gaa cag cgt acc gac ctg gac aag ctg gtc atc gaa atg gaa acc aac Glu Gln Arg Thr Asp Leu Asp Lys Leu Val Ile Glu Met Glu Thr Asn 195 200 205	624
ggc aca atc gat cct gaa gag gcg att cgt cgt gcg gca acc att ctg Gly Thr Ile Asp Pro Glu Glu Ala Ile Arg Arg Ala Ala Thr Ile Leu 210 215 220	672
gct gaa caa ctg gaa gct ttc gtt gac tta cgt gat gta cgt cag cct Ala Glu Gln Leu Glu Ala Phe Val Asp Leu Arg Asp Val Arg Gln Pro 225 230 235 240	720
gaa gtg aaa gag aaa cca gag ttc gat ccg atc ctg ctg cgc cct Glu Val Lys Glu Glu Lys Pro Glu Phe Asp Pro Ile Leu Leu Arg Pro 245 250 255	768
gtt gac gat ctg gaa ttg act gtc cgc tct gct aac tgc ctt aaa gca Val Asp Asp Leu Glu Leu Thr Val Arg Ser Ala Asn Cys Leu Lys Ala 260 265 270	816
gaa gct atc cac tat atc ggt gat ctg gta cag cgt acc gag gtt gag Glu Ala Ile His Tyr Ile Gly Asp Leu Val Gln Arg Thr Glu Val Glu 275 280 285	864
ctc ctt aaa acg cct aac ctt ggt aaa aaa tct ctt act gag att aaa Leu Leu Lys Thr Pro Asn Leu Gly Lys Lys Ser Leu Thr Glu Ile Lys 290 295 300	912
gac gtg ctg gct tcc cgt gga ctg tct ctg ggc atg cgc ctg gaa aac Asp Val Leu Ala Ser Arg Gly Leu Ser Leu Gly Met Arg Leu Glu Asn 305 310 315 320	960
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cgc cag gct atg ttc cgc aat atg gca ggt tca ctg gtt cgt cat gaa Arg Gln Ala Met Phe Arg Asn Met Ala Gly Ser Leu Val Arg His Glu 20 25 30	96
atc atc aag acg act ctg cct aaa gcg aaa gag ctg cgc cgc gta gtt Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val 35 40 45	144

gag ccg c Glu Pro I 50	-			_	_		-	_	_	-		_	_	192
ctg gca t Leu Ala I 65	-	-		_	_					-		_		240
aac gaa d Asn Glu l														288
att ctg a	aag tgt Lys Cys 100	ggc Gly	ttc Phe	cgt Arg	gca Ala	ggc Gly 105	gac Asp	aac Asn	gcg Ala	ccg Pro	atg Met 110	gct Ala	tac Tyr	336
atc gag of Ile Glu I													taa *	384
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gcg ctg a														96
ttc cca c Phe Pro C										Ser				144
										45				
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Leu Ala	Leu Ala att ggc	His	Phe ggt	Trp 55 gcc	Leu gga	Val att	Gly gct	Ile gtc	Ser 60 act	agt Ser cgc	Leu	Phe tgg	Ala ggc	192 240
Leu Ala 1 50 gtg atc a Val Ile 1	Leu Ala att ggc Ile Gly ttt cgc	His act Thr	ggt Gly 70 ctg	Trp 55 gcc Ala gtg	gga Gly gaa	Val att Ile act	Gly gct Ala att	gtc Val 75	Ser 60 act Thr	agt Ser cgc Arg	ccg Pro	tgg Trp	ggc Gly 80	
Leu Ala 1 50 gtg atc a Val Ile 1 65 gcg gaa 6	Leu Ala att ggc Ile Gly ttt cgc Phe Arg	His act Thr cca Pro 85	ggt Gly 70 ctg Leu	Trp 55 gcc Ala gtg Val	gga Gly gaa Glu	att Ile act Thr	gct Ala att Ile 90 gcc	gtc Val 75 gcc Ala	Ser 60 act Thr gcc Ala	agt Ser cgc Arg gtt Val	ccg Pro gga Gly	tgg Trp cag Gln 95	ggc Gly 80 act Thr	240

Gly	Leu	Gln 115	Pro	Ala	Ile	Ile	Ala 120	Leu	Ile	Leu	Tyr	Gly 125	Val	Leu	Pro		
gtc Val	ctg Leu 130	cag Gln	gcg Ala	aca Thr	ctt Leu	gcc Ala 135	ggg Gly	ctg Leu	gga Gly	gcg Ala	att Ile 140	gat Asp	gcc Ala	agc Ser	gtg Val		432
aca Thr 145	gaa Glu	gtt Val	gcg Ala	aaa Lys	ggt Gly 150	atg Met	gga Gly	atg Met	agt Ser	cgt Arg 155	ggt Gly	cag Gln	cga Arg	gtg Val	cgt Arg 160		480
aag Lys	gtc Val	gag Glu	cta Leu	ccg Pro 165	ctg Leu	gcg Ala	gct Ala	ccg Pro	gtg Val 170	att Ile	ctg Leu	gcg Ala	ggc Gly	gtg Val 175	cga Arg	·	528
act Thr	tcg Ser	gtg Val	att Ile 180	atc Ile	aac Asn	att Ile	ggt Gly	acg Thr 185	gcg Ala	acg Thr	atc Ile	gcc Ala	tca Ser 190	acg Thr	gta Val		576
ggg	gcc Ala	agc Ser 195	acg Thr	ctg Leu	ggt Gly	acg Thr	ccc Pro 200	atc Ile	atc Ile	atc Ile	ggg Gly	ctt Leu 205	agc Ser	gga Gly	ttt Phe		624
aat Asn	acc Thr 210	gcg Ala	tat Tyr	gtg Val	atc Ile	cag Gln 215	ggg Gly	gcg Ala	tta Leu	ctg Leu	gtg Val 220	gca Ala	ctg Leu	gcg Ala	gcg Ala		672
atc Ile 225	atc Ile	gca Ala	gac Asp	cgc Arg	ctg Leu 230	ttt Phe	gaa Glu	agg Arg	ctg Leu	gtg Val 235	cag Gln	gcg Ala	ctt Leu	agc Ser	cag Gln 240		720
	-	aaa Lys															732
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	1> C		. (92	7)													
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gtt Val	aac Asn	gat Asp	ctc Leu 20	Asn	ctc Leu	aat Asn	ttt Phe	cag Gln 25	Glu	Gly	agt Ser	ttt Phe	tcg Ser 30	Val	ctg Leu		96
att Ile	ggc Gly	aca Thr 35	Ser	ggc Gly	tcc Ser	ggc	aaa Lys 40	Ser	acc Thr	acc Thr	ctg Leu	aaa Lys 45	Met	att Ile	aac Asn		144
cgc Arg	ctg Leu	gtg Val	gag Glu	cat His	gac Asp	agc Ser	gga Gly	gag Glu	ato	cgc Arg	ttt Phe	gcc Ala	gga Gly	gaa Glu	gaa Glu		192

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300 290 295 927 ctg gtg gag gcg taa Leu Val Glu Ala \* 305 <210> 222 <211> 1158 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(1158) <400> 222 gtg act tat ttc cgt att aat cct gtt ctg gcg ctg ctg ctg ttg ctg 48 Met Thr Tyr Phe Arg Ile Asn Pro Val Leu Ala Leu Leu Leu Leu acg gca atc gca gcg gcg ctg ccg ttt atc agt tac gcg cct aat cgt 96 Thr Ala Ile Ala Ala Ala Leu Pro Phe Ile Ser Tyr Ala Pro Asn Arg 25 tta gtt tcg ggt gag ggg cgt cat ctc tgg cag ctg tgg ccg caa acg 144 Leu Val Ser Gly Glu Gly Arg His Leu Trp Gln Leu Trp Pro Gln Thr atc tgg atg ctg gtg ggc gtt ggt tgc gcc tgg ctg acg gcc tgt ttt 192 Ile Trp Met Leu Val Gly Val Gly Cys Ala Trp Leu Thr Ala Cys Phe 240 att ccc ggt aaa aaa ggc agc att tgt gca ctc att ctg gcg caa ttc Ile Pro Gly Lys Lys Gly Ser Ile Cys Ala Leu Ile Leu Ala Gln Phe gtc ttc gta ttg ctg gtg tgg gga gct gga aag gcg gcg acc caa ctg 288 Val Phe Val Leu Leu Val Trp Gly Ala Gly Lys Ala Ala Thr Gln Leu 90 336 gcg caa aat ggc agt gcg ctg gcg cgt acc agc ctc ggc agt ggt ttc Ala Gln Asn Gly Ser Ala Leu Ala Arg Thr Ser Leu Gly Ser Gly Phe tgg ctg gct gcg gcg ctg gca ttg ctg gcc tgt agc gat gcc atc cgc 384 Trp Leu Ala Ala Leu Ala Leu Leu Ala Cys Ser Asp Ala Ile Arg 120 432 cga atc tcc acg cat ccg ctg tgg cgc tgg ttg ttg cat atg cag att Arg Ile Ser Thr His Pro Leu Trp Arg Trp Leu Leu His Met Gln Ile 135 gcc att att ccg ctg tgg ttg ctg tac tcc ggc acg ctt aac gat ctc 480 Ala Ile Ile Pro Leu Trp Leu Leu Tyr Ser Gly Thr Leu Asn Asp Leu 150 155

170

tca cta atg aaa gaa tac gcc aac cgt cag gat gtg ttt gac gac gcg Ser Leu Met Lys Glu Tyr Ala Asn Arg Gln Asp Val Phe Asp Asp Ala

165

528

ctg gc Leu Al															576
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cag gg Gln Gl 21	y Ala	att Ile	ttt Phe	tct Ser	ctg Leu 215	ctc Leu	aat Asn	gtg Val	att Ile	cag Gln 220	acc Thr	gtg Val	cct Pro	tcg Ser	672
gtg gc Val Al 225	g ctc a Leu	ttt Phe	ggc Gly	ctg Leu 230	ttg Leu	att Ile	gcg Ala	ccg Pro	ctt Leu 235	gcc Ala	gcg Ala	ctg Leu	gtt Val	acg Thr 240	720
gcc tt Ala Ph															768
ccc gc Pro Al															816
ggc gt Gly Va															864
gcc ag Ala Ar 29	g Ālā														912
tta co Leu Pr 305															960
gtg ca Val Gl	a act n Thr	gta Val	ggt Gly 325	atg Met	gcg Ala	gtg Val	att Ile	gcg Ala 330	gcg Ala	tta Leu	atc Ile	ggc Gly	gca Ala 335	ggc Gly	1008
ggt tt Gly Ph															1056
tta gt Leu Va	g ttg l Leu 355	Leu	ggg	gtg Val	atc Ile	ccg Pro 360	gta Val	att Ile	gtt Val	ctg Leu	gcg Ala 365	gtg Val	ctt Leu	acc Thr	1104
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gat to Asp * 385	a														1158

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gtg Val	agc Ser	ctg Leu	ccg Pro 20	cta Leu	cag Gln	gcg Ala	gct Ala	tcc Ser 25	ccc Pro	gtt Val	aaa Lys	gtc Val	ggt Gly 30	tca Ser	aaa Lys	96
atc Ile	gat Asp	acc Thr 35	gaa Glu	ggt Gly	gcg Ala	cta Leu	ctc Leu 40	ggc Gly	aat Asn	atc Ile	att Ile	ttg Leu 45	cag Gln	gtg Val	ctg Leu	144
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cct Pro 65	gtg Val	gtg Val	cgc Arg	ggg Gly	gcg Ala 70	att Ile	act Thr	tcc Ser	ggt Gly	gaa Glu 75	ctg Leu	gat Asp	atc Ile	tat Tyr	ccg Pro 80	240
gaa Glu	tat Tyr	acc Thr	ggc Gly	aat Asn 85	ggc Gly	gct Ala	ttc Phe	ttc Phe	ttt Phe 90	aaa Lys	gat Asp	gaa Glu	aac Asn	gat Asp 95	gca Ala	288
gcg Ala	tgg Trp	aaa Lys	aac Asn 100	gcg Ala	cag Gln	caa Gln	ggt Gly	tac Tyr 105	gag Glu	aaa Lys	gtc Val	aaa Lys	aag Lys 110	ctc Leu	gat Asp	336
tcg Ser	gag Glu	cac His 115	aac Asn	aag Lys	tta Leu	atc Ile	tgg Trp 120	ctg Leu	acg Thr	ccc Pro	gcg Ala	cct Pro 125	gca Ala	aat Asn	aac Asn	384
acc Thr	tgg Trp 130	act Thr	atc Ile	gcc Ala	gtg Val	cgt Arg 135	cag Gln	gat Asp	gtg Val	gca Ala	gag Glu 140	aaa Lys	aat Asn	aaa Lys	ctc Leu	432
act Thr 145	tcg Ser	ctt Leu	gcc Ala	gac Asp	ctg Leu 150	agt Ser	cgt Arg	tat Tyr	ctg Leu	caa Gln 155	gag Glu	ggc Gly	ggc Gly	acc Thr	ttc Phe 160	480
aaa Lys	ctg Leu	gca Ala	gcc Ala	tcg Ser 165	Ala	gag Glu	ttt Phe	atc Ile	gaa Glu 170	Arg	gcc Ala	gat Asp	gcg Ala	tta Leu 175	ccc Pro	528
gcg Ala	ttt Phe	gaa Glu	aaa Lys 180	gcc Ala	tat Tyr	ggc Gly	ttt Phe	aag Lys 185	ctc Leu	ggt Gly	cag Gln	gat Asp	cag Gln 190	ttg Leu	ctg Leu	576
tca Ser	ctg Leu	gct Ala 195	Gly	ggc Gly	gac Asp	acg Thr	gcg Ala 200	Val	acg Thr	atc Ile	aaa Lys	gcc Ala 205	Ala	gcc Ala	cag Gln	624

Gln	acc Thr 210	tct Ser	ggc Gly	gtt Val	aat Asn	gct Ala 215	gca Ala	atg Met	gct Ala	tac Tyr	ggc Gly 220	act Thr	gac Asp	ggc Gly	ccg Pro	672
gta Val 225	gcg Ala	gcg Ala	ctg Leu	G1y ggg	ctg Leu 230	caa Gln	acc Thr	tta Leu	agc Ser	gat Asp 235	ccg Pro	caa Gln	ggt Gly	gtg Val	caa Gln 240	720
cct Pro	atc Ile	tac Tyr	gcg Ala	cct Pro 245	gca Ala	cca Pro	gtg Val	gtg Val	cgt Arg 250	gag Glu	tcc Ser	gtg Val	ttg Leu	agg Arg 255	gag Glu	768
tat Tyr	ccg Pro	caa Gln	atg Met 260	gca Ala	cag Gln	tgg Trp	cta Leu	cag Gln 265	cca Pro	gtc Val	ttc Phe	gcc Ala	agc Ser 270	ctc Leu	gat Asp	816
gca Ala	aaa Lys	aca Thr 275	ttg Leu	cag Gln	caa Gln	ctg Leu	aat Asn 280	gcc Ala	agc Ser	att Ile	gct Ala	gtg Val 285	gaa Glu	gga Gly	ctg Leu	864
.gat Asp	gcc Ala 290	aaa Lys	aaa Lys	gtg Val	gct Ala	gcc Ala 295	gac Asp	tac Tyr	ctg Leu	aaa Lys	caa Gln 300	aaa Lys	ggg Gly	tgg Trp	acg Thr	912
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Gln	Pro	Arg	Arg	Leu 85	Pro	Lys	Trp	Met	Leu 90	Pro	Val	Leu	Asp	Ala 95	Val	
ggt Gly	ctg Leu	gcg Ala	gtg Val 100	ttt Phe	gtc Val	ggc Gly	att Ile	ggc Gly 105	gtg Val	aat Asn	aaa Lys	gcc Ala	ttt Phe 110	aat Asn	gcg Ala	336
gaa Glu	gcc Ala	ggt Gly 115	ccg Pro	tta Leu	atc Ile	gcg Ala	gtt Val 120	tgt Cys	atg Met	ggc Gly	gtc Val	att Ile 125	act Thr	ggc Gly	gtt Val	384
ggc Gly	ggc Gly 130	ggg Gly	atc Ile	att Ile	cgt Arg	gat Asp 135	gtt Val	ctg Leu	gcc Ala	cgc Arg	gaa Glu 140	atc Ile	ccc Pro	atg Met	att Ile	432
tta Leu 145	cgt Arg	aca Thr	gaa Glu	atc Ile	tac Tyr 150	gca Ala	act Thr	gcc Ala	tgt Cys	att Ile 155	atc Ile	ggc Gly	ggt Gly	att Ile	gtc Val 160	480
cac His	gct Ala	acg Thr	gct Ala	tat Tyr 165	tac Tyr	aca Thr	ttt Phe	tcc Ser	gta Val 170	cca Pro	ctg Leu	gaa Glu	aca Thr	gcc Ala 175	agt Ser	528
atg Met	atg Met	ggc Gly	atg Met 180	gtc Val	gtg Val	acg Thr	cta Leu	ttg Leu 185	att Ile	cgg Arg	ctg Leu	gcg Ala	gct Ala 190	att Ile	cgt Arg	576
tgg Trp	cat His	ctt Leu 195	aag Lys	cta Leu	ccg Pro	acg Thr	ttt Phe 200	gcg Ala	ctg Leu	gat Asp	gag Glu	aat Asn 205	ggg Gly	cgt Arg	tga *	624
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cca Pro	ctg Leu	tgg Trp	ctc Leu 20	aac Asn	gcc Ala	gcg Ala	ccg Pro	cgc Arg 25	Val	atc Ile	acg Thr	ctt Leu	tct Ser 30	Pro	gcc Ala	96
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ago Ser	tat Tyr	Ser	gac Asp	tat Tyr	cct Pro	cca Pro	Gln	gcg Ala	caa Gln	aag Lys	att Ile	Glu	cag Gln	gtt Val	tcc Ser	192

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			gcc Ala													:	288
			ctg Leu 100													:	336
			gcc Ala													,	384
cca Pro	gac Asp 130	aag Lys	gcc Ala	gaa Glu	caa Gln	gcc Ala 135	gcg Ala	caa Gln	tcc Ser	ctg Leu	ctg Leu 140	gat Asp	cag Gln	tac Tyr	gcg Ala		432
			gcg Ala														480
			att Ile														528
			ctc Leu 180														576
			tgg Trp														624
			att Ile														672
aaa Lys 225	caa Gln	tac Tyr	tgg Trp	ggt Gly	gaa Glu 230	cag Gln	ctc Leu	aaa Lys	att Ile	ccc Pro 235	gtt Val	att Ile	cct Pro	ctc Leu	acg Thr 240		720
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			aat Asn 260														801
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cgt Arg	gac Asp	aaa Lys	atc Ile 20	gaa Glu	aac Asn	cgt Arg	caa Gln	act Thr 25	atc Ile	agt Ser	ctc Leu	ggc Gly	ggt Gly 30	tgc Cys	gaa Glu	96
atc Ile	tat Tyr	acc Thr 35	ggc Gly	caa Gln	ctg Leu	aat Asn	gga Gly 40	acc Thr	gag Glu	gtt Val	gcg Ala	ctt Leu 45	ctg Leu	aaa Lys	tcg Ser	144
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cac His 65	tgc Cys	aag Lys	cca Pro	gat Asp	gtg Val 70	att Ile	att Ile	aac Asn	acc Thr	ggt Gly 75	tct Ser	gcc Ala	ggt Gly	ggc Gly	ctg Leu 80	240
gca Ala	cca Pro	acg Thr	ttg Leu	aaa Lys 85	gtg Val	ggc Gly	gat Asp	atc Ile	gtt Val 90	gtc Val	tcg Ser	gac Asp	gaa Glu	gca Ala 95	cgt Arg	288
tat Tyr	cac His	gac Asp	gcg Ala 100	gat Asp	gtc Val	acg Thr	gca Ala	ttt Phe 105	ggt Gly	tat Tyr	gaa Glu	tac Tyr	ggt Gly 110	cag Gln	tta Leu	336
cca Pro	ggc Gly	tgt Cys 115	ccg Pro	gca Ala	ggc Gly	ttt Phe	aaa Lys 120	gct Ala	gac Asp	gat Asp	aaa Lys	ctg Leu 125	atc Ile	gct Ala	gcc Ala	384
gct Ala	gag Glu 130	gcc Ala	tgc Cys	att Ile	gcc Ala	gaa Glu 135	ctg Leu	aat Asn	ctt Leu	aac Asn	gct Ala 140	gta Val	cgt Arg	ggc Gly	ctg′ Leu	432
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gca Ala	atc Ile	gcc Ala	cat His 180	gtc Val	tgc Cys	cac His	aat Asn	ttc Phe 185	aac Asn	gtc Val	ccg Pro	ttt Phe	gtt Val 190	gtc Val	gta Val	576
cgc Arg	gcc Ala	atc Ile 195	tcc Ser	gac Asp	gtg Val	gcc Ala	gat Asp 200	Gln	cag Gln	tct Ser	cat His	ctt Leu 205	Ser	ttc Phe	gat Asp	624
gag Glu	ttc Phe 210	Leu	gct Ala	gtt Val	gcc Ala	gct Ala 215	aaa Lys	cag Gln	tcc Ser	agc Ser	ctg Leu 220	Met	gtt Val	gag Glu	tca Ser	672
	Val		aaa Lys			His										699

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gga Gly	ccc Pro	cat His 35	gtc Val	gaa Glu	att Ile	ggt Gly	gag Glu 40	ggt Gly	acc Thr	gta Val	ctg Leu	aaa Lys 45	tct Ser	cac His	gtt Val	144
	gtg Val 50															192
	gcc Ala															240
	acc Thr															288
	att Ile															336
	gac Asp															384
	ggt Gly 130															432
	tcg Ser															480
	ttc Phe															528
	gcg Ala															576

acg Thr	ccg Pro	ttc Phe 195	ggt Gly	gtc Val	aat Asn	atc Ile	gaa Glu 200	ggg Gly	ctg Leu	aag Lys	cgc Arg	cgc Arg 205	gga Gly	ttc Phe	agc Ser	624
cgt Arg	gag Glu 210	gcg Ala	att Ile	acc Thr	gct Ala	atc Ile 215	cgc Arg	aat Asn	gcg Ala	tat Tyr	aag Lys 220	ctg Leu	att Ile	tat Tyr	cgt Arg	672
agc Ser 225	ggt Gly	aaa Lys	acg Thr	ctc Leu	gat Asp 230	gaa Glu	gtg Val	aaa Lys	ccg Pro	gaa Glu 235	att Ile	gct Ala	gaa Glu	ctg Leu	gcg Ala 240	720
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Asp	ctg Leu	Thr	Lys cct	Arg 85 gac Asp	ttt Phe	Gly	Glu att	Leu act	Lys 90 ctt	Pro	Asp ggt	Val	Phe	Val 95 aaa Lys	Gly	288 336

Gln	Gly	Ile 115	Lys	Thr	Ile	His	Tyr 120	Val	Ser	Pro	Ser	Val 125	Trp	Ala	Trp	
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Ala	Met	His 355	Asp	Thr	Phe	Arg	Glu 360	Leu	His	Gln	Gln	11e 365	Arg	Cys	Asn	
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	l> CI	os L)	. (597	7)												
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		gga Gly														96
		gac Asp 35														144
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		agc Ser														240
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atg atc gat ggc Met Ile Asp Gly 20	Leu Ala Lys T	acc gca ccg ttg o Thr Ala Pro Leu V 25	gta aaa aag gcg Val Lys Lys Ala 30	gcg 96 Ala
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		gcg gcg aac aat a Ala Ala Asn Asn ' 90		
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ggg ccg atc atc Gly Pro Ile Ile 115	Asp Arg Asp T	tgg ctt atc gaa f Frp Leu Ile Glu 1 120	tta aac gaa ggg Leu Asn Glu Gly 125	ttg 384 Leu
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-174-

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gat Asp	gaa Glu	gaa Glu	agc Ser 180	tat Tyr	ctg Leu	cac His	gcg Ala	gcg Ala 185	gtg Val	gaa Glu	ctg Leu	gcg Ala	gaa Glu 190	gcg Ala	cgc Arg	576
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gac Asp	ttt Phe 210	gac Asp	gca Ala	cac His	gaa Glu	atc Ile 215	cgc Arg	gtc Val	gcg Ala	atc Ile	cac His 220	gac Asp	ggc Gly	ttt Phe	acc Thr	672
ctc Leu 225	gac Asp	gat Asp	cct Pro	aaa Lys	cgc Arg 230	ccg Pro	cgt Arg	aac Asn	tat Tyr	tcg Ser 235	ccg Pro	cag Gln	caa Gln	tat Tyr	atg Met 240	720
cgt Arg	agc Ser	gaa Glu	gag Glu	gag Glu 245	atg Met	tgt Cys	gag Glu	ctg Leu	ttt Phe 250	gcc Ala	gac Asp	atc Ile	Pro	gaa Glu 255	gcc Ala	768
ctt Leu	gcc Ala	aac Asn	acc Thr 260	gtt Val	gag Glu	atc Ile	gcc Ala	aaa Lys 265	cgc Arg	tgt Cys	aac Asn	gta Val	acc Thr 270	gtg Val	cgt Arg	816
					ctg Leu											864
					aag Lys											912
gcc Ala 305	ttt Phe	tta Leu	ttc Phe	cct Pro	gat Asp 310	gag Glu	gaa Glu	gaa Glu	cgt Arg	ctt Leu 315	aag Lys	cgc Arg	cgc Arg	ccg Pro	gaa Glu 320	960
tat Tyr	gac Asp	gaa Glu	cgt Arg	ctg Leu 325	gag Glu	act Thr	gaa Glu	ctt Leu	cag Gln 330	gtt Val	atc Ile	aac Asn	cag Gln	atg Met 335	ggc Gly	1008
ttc Phe	ccg Pro	ggc Gly	tac Tyr 340	ttc Phe	ctc Leu	atc Ile	gtt Val	atg Met 345	gaa Glu	ttt Phe	atc Ile	cag Gln	tgg Trp 350	tcg Ser	aaa Lys	1056
gat Asp	aac Asn	ggc Gly 355	gta Val	ccg Pro	gta Val	Gly	cca Pro 360	ggc	cgt Arg	ggc	tcc Ser	ggt Gly 365	gcg Ala	ggt Gly	tca Ser	1104
ctg Leu	gtg Val 370	gcc Ala	tac Tyr	gcg Ala	ctg Leu	aaa Lys 375	atc Ile	acc Thr	gac Asp	ctc Leu	gat Asp 380	ccg Pro	ctg Leu	gaa Glu	ttt Phe	1152
gac Asp 385	Leu	ctg Leu	ttc Phe	gaa Glu	cgt Arg 390	ttc Phe	ctt Leu	aac Asn	ccg Pro	gaa Glu 395	cgt Arg	gtc Val	tcc Ser	atg Met	cct Pro 400	1200

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								gat Asp 425								1296	6
ttc Phe	ggt Gly	aca Thr 435	atg Met	gcg Ala	gcg Ala	aaa Lys	gcg Ala 440	gtg Val	atc Ile	cgc Arg	gac Asp	gta Val 445	ggc Gly	cgc Arg	gtg Val	134	4
ctg Leu	ggg Gly 450	cat His	ccg Pro	tac Tyr	ggc Gly	ttt Phe 455	gtc Val	gat Asp	cgt Arg	atc Ile	tcg Ser 460	aaa Lys	ctg Leu	atc Ile	ccg Pro	1392	2
ccc Pro 465	gat Asp	ccg Pro	ggg Gly	atg Met	acg Thr 470	ctg Leu	gcg Ala	aaa Lys	gcg Ala	ttt Phe 475	gaa Glu	gcc Ala	gag Glu	ccg Pro	cag Gln 480	1440	0
ctg Leu	ccg Pro	gaa Glu	atc Ile	tac Tyr 485	gaa Glu	gcg Ala	gat Asp	gaa Glu	gaa Glu 490	gtt Val	aag Lys	gcg Ala	ctg Leu	atc Ile 495	gac Asp	148	В
atg Met	gcg Ala	cgc Arg	aaa Lys 500	ctg Leu	gaa Glu	ggg Gly	gtc Val	acc Thr 505	cgt Arg	aac Asn	gcc Ala	ggt Gly	aag Lys 510	cac His	gcc Ala	153	6
ggt Gly	G1 y ggg	gtg Val 515	gtt Val	atc Ile	gcg Ala	ccg Pro	acc Thr 520	aaa Lys	att Ile	acc Thr	gat Asp	ttt Phe 525	gcg Ala	ccg Pro	ctt Leu	158	4
tac Tyr	tgc Cys 530	gat Asp	gaa Glu	gag Glu	ggc Gly	aaa Lys 535	cat His	ccg Pro	gtc Val	acc Thr	cag Gln 540	ttt Phe	gat Asp	aaa Lys	agc Ser	163	2
gac Asp 545	gtt Val	gaa Glu	tac Tyr	gcc Ala	gga Gly 550	ctg Leu	gtg Val	aag Lys	ttc Phe	gac Asp 555	ttc Phe	ctt Leu	ggt Gly	ttg Leu	cgt Arg 560	168	0
acg Thr	ctc Leu	acc Thr	atc Ile	atc Ile 565	aac Asn	tgg Trp	gcg Ala	ctg Leu	gag Glu 570	atg Met	atc Ile	aac Asn	aag Lys	cgg Arg 575	cgg Arg	172	8
gcg Ala	aag Lys	aat Asn	ggc Gly 580	gag Glu	ccg Pro	ccg Pro	ctg Leu	gat Asp 585	atc Ile	gct Ala	gċg Ala	atc Ile	ccg Pro 590	ctg Leu	gat Asp	177	6
gat Asp	aag Lys	aaa Lys 595	agc Ser	ttc Phe	gac Asp	atg Met	ctg Leu 600	caa Gln	cgc Arg	tcg Ser	gaa Glu	acc Thr 605	acg Thr	gcg Ala	gta Val	182	4
ttc Phe	cag Gln 610	ctt Leu	gaa Glu	tcg Ser	cgc Arg	ggc Gly 615	atg Met	aag Lys	gac Asp	ctg Leu	atc Ile 620	aag Lys	cgt Arg	cta Leu	caa Gln	187	2
cct Pro 625	gac Asp	tgc Cys	ttc Phe	gaa Glu	gat Asp 630	atg Met	atc Ile	gcc Ala	cta Leu	gtg Val 635	gca Ala	ctg Leu	ttc Phe	cgc Arg	ccc Pro 640	192	0

						atg Met										19	968
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						cca Pro										20	)64
cag Gln	gtc Val 690	atg Met	cag Gln	att Ile	gcg Ala	cag Gln 695	gtg Val	ctt Leu	tct Ser	ggt Gly	tat Tyr 700	acc Thr	ctc Leu	ggt Gly	ggc Gly	21	112
gcg Ala 705	gat Asp	atg Met	ctg Leu	cgt Arg	cgt Arg 710	gcg Ala	atg Met	ggt Gly	aag Lys	aaa Lys 715	aag Lys	ccg Pro	gaa Glu	gag Glu	atg Met 720	21	160
gct Ala	aag Lys	caa Gln	cgt Arg	tct Ser 725	gta Val	ttt Phe	gct Ala	gaa Glu	ggt Gly 730	gca Ala	gaa Glu	aag Lys	aac Asn	gga Gly 735	atc Ile	22	808
aac Asn	gct Ala	gaa Glu	ctg Leu 740	gcg Ala	atg Met	aaa Lys	atc Ile	ttc Phe 745	gac Asp	ctg Leu	gtg Val	gag Glu	aaa Lys 750	ttc Phe	gct Ala	22	256
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tat Tyr	caa Gln 770	acg Thr	tta Leu	tgg Trp	ctg Leu	aaa Lys 775	gcg Ala	cac His	tat Tyr	cct Pro	gcg Ala 780	gag Glu	ttt Phe	atg Met	gcg Ala	23	352
gcg Ala 785	gta Val	atg Met	acc Thr	gcc Ala	gat Asp 790	atg Met	gac Asp	aac Asn	acc Thr	gag Glu 795	aag Lys	gtg Val	gtg Val	ggt Gly	ctg Leu 800	24	100
						atg Met										24	148
aac Asn	tcc Ser	ggt Gly	ctt Leu 820	tac Tyr	cat His	ttc Phe	cac His	gtc Val 825	aac Asn	gac Asp	gac Asp	ggc Gly	gaa Glu 830	atc Ile	gtg Val	24	196 .
tat Tyr	ggt Gly	att Ile 835	ggc Gly	gcg Ala	atc Ile	aaa Lys	ggg Gly 840	gtc Val	ggt Gly	gaa Glu	ggt Gly	ccg Pro 845	att Ile	gag Glu	gcc Ala	25	544
atc Ile	atc Ile 850	gaa Glu	gcc Ala	cgt Arg	aat Asn	aaa Lys 855	ggc Gly	ggc Gly	tac Tyr	ttc Phe	cgc Arg 860	gaa Glu	ctg Leu	ttt Phe	gat Asp	2	592
ctc Leu 865	tgc Cys	gcc Ala	cgt Arg	acc Thr	gac Asp 870	acc Thr	aaa Lys	aag Lys	ttg Leu	aac Asn 875	cgt Arg	cgc Arg	gtg Val	ctg Leu	gaa Glu 880	2	640

::-

aaa ct Lys Le	tg atc eu Ile	atg Met	tcc Ser 885	ggg Gly	gcg Ala	ttt Phe	gac Asp	cgt Arg 890	ctt Leu	ggg Gly	cca Pro	cat His	cgc Arg 895	gca Ala	2688
gcg ct Ala Le	tg atg eu Met	aac Asn 900	tcg Ser	ctg Leu	ggc Gly	gat Asp	gcg Ala 905	tta Leu	aaa Lys	gcg Ala	gca Ala	gat Asp 910	caa Gln	cac His	2736
gcg aa Ala Ly	aa gcg ys Ala 915	gaa Glu	gct Ala	atc Ile	ggt Gly	cag Gln 920	gcc Ala	gat Asp	atg Met	ttc Phe	ggc Gly 925	gtg Val	ctg Leu	gcc Ala	2784
Glu Gl	ag ccg lu Pro 30														2832
ccg ga Pro Gl 945	ag cag lu Gln	gtg Val	gta Val	tta Leu 950	gat Asp	ggg Gly	gaa Glu	cgt Arg	gaa Glu 955	acg Thr	tta Leu	ggc Gly	ctg Leu	tac Tyr 960	2880
ctg ac Leu Th	cc gga hr Gly	cac His	cct Pro 965	atc Ile	aac Asn	cag Gln	tat Tyr	tta Leu 970	aaa Lys	gag Glu	att Ile	gag Glu	cgt Arg 975	tat Tyr	2928
gtc gg Val G	ga ggc ly Gly	gta Val 980	agg Arg	ctg Leu	aaa Lys	gac Asp	atg Met 985	cac His	ccg Pro	aca Thr	gaa Glu	cgt Arg 990	ggt Gly	aaa Lys	2976
gtc at Val II	tc acg le Thr 99	Ala	gcg Ala	ggg Gly	ctc Leu	gtt Val 1000	Val	gcc Ala	gcg Ala	cgg Arg	gtt Val 1009	Met	gtc Val	acc Thr	3024
Lys A	gc ggc rg Gly 010	aat Asn	cgt Arg	atc Ile	ggt Gly 101!	Ile	tgc Cys	acg Thr	ctg Leu	gat Asp 1020	Asp	cgt Arg	tcc Ser	Gly ggg	3072
cgg ct Arg Le 1025	tg gaa eu Glu	gtg Val	atg Met	ttg Leu 1030	Phe	act Thr	gac Asp	gcc Ala	ctg Leu 103	Asp	aaa Lys	tac Tyr	cag Gln	caa Gln 1040	3120
	tg gaa eu Glu			Arg					Ser					Phe	3168
gat ga Asp As	ac ttc sp Phe	agc Ser 106	Gly	ggg	ctt Leu	aaa Lys	atg Met 106	Thr	gct Ala	cgc Arg	gaa Glu	gtg Val 107	Met	gat Asp	3216
att ga Ile A	ac gaa sp Glu 107	Ala	cgg Arg	gaa Glu	aaa Lys	tat Tyr 108	Ala	cgc Arg	ggg Gly	ctt Leu	gct Ala 108	Ile	tcg Ser	ctg Leu	3264
Thr A	gac agg Asp Arg .090					Gln					Leu				3312
ctg g Leu G 1105	gaa ccc Slu Pro	cac His	cgc Arg	tct Ser 111	Gly	aca Thr	att Ile	cca Pro	gta Val 111	His	ctc Leu	tac Tyr	tat Tyr	cag Gln 1120	3360

agg gcg gat gca cgc gcg cgg ttg cgt ttt ggc gcg acg tgg cgt gtc Arg Ala Asp Ala Arg Ala Arg Leu Arg Phe Gly Ala Thr Trp Arg Val 1125 1130 1135	3408
tct ccg agc gat cgt tta tta aac gat ctc cgt ggc ctc att ggt tcg Ser Pro Ser Asp Arg Leu Leu Asn Asp Leu Arg Gly Leu Ile Gly Ser 1140 1145 1150	3456
gag cag gtg gaa ctg gag ttt gac taa Glu Gln Val Glu Leu Glu Phe Asp * 1155 1160	3483
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aga atg gca cga gac tcc gtg ctg cta ctg gaa aaa ctc ggc tgt cgc Arg Met Ala Arg Asp Ser Val Leu Leu Leu Glu Lys Leu Gly Cys Arg 20 25 30	96
gta aat ttc ccg gag aaa cag gga tgc tgc ggt cag cct gcg atc aat Val Asn Phe Pro Glu Lys Gln Gly Cys Cys Gly Gln Pro Ala Ile Asn 35 40 45	144
agc ggt tat atc aaa gaa gcg att cca ggg atg aaa aat ctg atc gcc Ser Gly Tyr Ile Lys Glu Ala Ile Pro Gly Met Lys Asn Leu Ile Ala 50 55 60	192
gca ctg gag gat aac gac gat ccc att att tca ccg gct ggc tct tgc Ala Leu Glu Asp Asn Asp Asp Pro Ile Ile Ser Pro Ala Gly Ser Cys 65 70 75 80	240
acc tat gcc gta aaa agt tac ccg acg tat ctg gcg gat gaa cct gaa Thr Tyr Ala Val Lys Ser Tyr Pro Thr Tyr Leu Ala Asp Glu Pro Glu 85 90 95	288
tgg gca tca cgt gcc gca aag gtt gcc gcg cgt atg cag gat ctc acc Trp Ala Ser Arg Ala Ala Lys Val Ala Ala Arg Met Gln Asp Leu Thr 100 105 110	336
tct ttt att gtt aat aaa tta ggg gta gtc gat gta ggt gcc agt ttg Ser Phe Ile Val Asn Lys Leu Gly Val Val Asp Val Gly Ala Ser Leu 115 120 125	384
caa ggg aga gcg gtg tat cac cca tct tgt agc ctg gcc cgt aag ctg Gln Gly Arg Ala Val Tyr His Pro Ser Cys Ser Leu Ala Arg Lys Leu 130 135 140	432

Gly Val Lys 145	gac gag Asp Glu		_	-	_				_		-	480
gag ctg ttg Glu Leu Leu			_	-		_	-					528
acg ttc tcg Thr Phe Ser												576
aag gtt gcg Lys Val Ala 195												624
gac gtg agt Asp Val Ser 210	-		n Ile	_		_				_		672
cag aaa gtc Gln Lys Val 225		_		-	-		_	-	_	-	tga *	720
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<pre>&lt;221&gt; CDS &lt;222&gt; (1) &lt;400&gt; 232 atg tcg atc Met Ser Ile 1 caa att gaa Gln Ile Glu  cgt att ggg Arg Ile Gly</pre>	aaa acc Lys Thr 5 gat ccg Asp Pro 20 gca aat Ala Asn cgc gat Arg Asp	atc at Ile Me cgg ca Arg Gl cgg gc Arg Al 5	g cgc t Arg a aaa n Lys 40 c gcc a Ala 5	aaa Lys 25 atg Met cag Gln	Phe 10 gcg Ala gtc Val ata Ile tca	gtg Val gat Asp cgt Arg	Thr gca Ala gaa Glu gat Asp 60 aaa	aac Asn ttg Leu 45 cat His	gcg Ala 30 ggg Gly gtt Val	Arg 15 cag Gln cac His ctg Leu	cag Gln tgg Trp agt Ser	96 144
<pre>&lt;221&gt; CDS &lt;222&gt; (1) &lt;400&gt; 232 atg tcg atc Met Ser Ile 1  caa att gaa Gln Ile Glu  cgt att ggg Arg Ile Gly</pre>	aaa acc Lys Thr 5  gat ccg Asp Pro 20  gca aat Ala Asn  cgc gat Arg Asp  gct tat Ala Tyr	atc at Ile Me cgg ca Arg Gl cgg gc Arg Al 5 ctg ta Leu Ty 70 ttt gc	g cgc t Arg a aaa n Lys 40 c gcc a Ala 5 c cag r Gln a aga	aaa Lys 25 atg Met cag Gln ctc Leu	Phe 10 gcg Ala gtc Val ata Ile tca Ser	gtg Val gat Asp cgt Arg gaa Glu 75	gca Ala gaa Glu gat Asp 60 aaa Lys	aac Asn ttg Leu 45 cat His gtg Val	gcg Ala 30 ggg Gly gtt Val acg Thr	Arg 15 cag Gln cac His ctg Leu caa Gln cgc	cag Gln tgg Trp agt Ser aac Asn 80 tac	96 144 192

Ile	Leu	Gln	Val 100	Ala	Gln	Arg	Lys	Asn 105	Ala	Arg	Lys	Val	Val 110	Lys	Ser	
aaa Lys	tcg Ser	atg Met 115	gtg Val	acc Thr	gaa Glu	gag Glu	att Ile 120	ggt Gly	gtc Val	aat Asn	cat His	gtg Val 125	ttg Leu	cag Gln	gat Asp	384
gct Ala	ggc Gly 130	att Ile	cag Gln	gtg Val	att Ile	gaa Glu 135	acc Thr	gat Asp	ctg Leu	ggt Gly	gaa Glu 140	tat Tyr	att Ile	ctc Leu	cag Gln	432
ctg Leu 145	gat Asp	caa Gln	gat Asp	ccg Pro	cca Pro 150	tct Ser	cat His	gtt Val	gtg Val	gtc Val 155	ccg Pro	gca Ala	att Ile	cat His	aaa Lys 160	480
gat Asp	cgc Arg	cat His	cag Gln	atc Ile 165	cgt Arg	cga Arg	gtg Val	cta Leu	cac His 170	gaa Glu	cgt Arg	ctg Leu	ggc Gly	tat Tyr 175	gag Glu	528
Gly	ccg Pro	gaa Glu	acg Thr 180	cct Pro	gaa Glu	gcg Ala	atg Met	acc Thr 185	tta Leu	ttc Phe	atc Ile	cgg Arg	caa Gln 190	aaa Lys	atc Ile	576
cgc Arg	gaa Glu	gat Asp 195	ttc Phe	ctc Leu	agt Ser	gct Ala	gaa Glu 200	ata Ile	ggt Gly	att Ile	acc Thr	ggc Gly 205	tgt Cys	aat Asn	ttc Phe	624
gcg Ala	gtg Val 210	gca Ala	gag Glu	acc Thr	ggt Gly	tcg Ser 215	gta Val	tgc Cys	ctg Leu	gtg Val	acc Thr 220	aat Asn	gaa Glu	ggt Gly	aat Asn	672
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atg Met	ctg Leu	gcg Ala	cgc Arg 260	agt Ser	gcc Ala	gtt Val	ggt Gly	gca Ala 265	cgt Arg	ttg Leu	acg Thr	gga Gly	tac Tyr 270	Asn	acc Thr	816
tgg Trp	ctg Leu	aca Thr 275	Gly	ccg Pro	cgc Arg	gaa Glu	gct Ala 280	Gly	cac His	gtt Val	gat Asp	ggt Gly 285	cct Pro	gaa Glu	gag Glu	864
ttt Phe	cat His 290	Leu	gtt Val	att Ile	gtc Val	gat Asp 295	Asn	ggg	cgt Arg	tct Ser	gag Glu 300	Val	ctg Leu	gcc Ala	tct Ser	912
gaa Glu 305	Phe	cgg Arg	gat Asp	gtg Val	ctg Leu 310	Arg	tgt Cys	att	cgc	tgc Cys 315	Gly	gct Ala	tgt Cys	atg Met	aat Asn 320	960
act Thr	tgt Cys	ccg Pro	gca Ala	tat Tyr 325	Arg	cat His	att	ggc Gly	ggt Gly 330	His	gga Gly	tat Tyr	ggc	tct Ser 335	att	1008
tat	сса	ggg	сса	att	ggt	gcg	gtg	att	tct	ccg	, cta	ctt	ggc	ggc	tat	1056

Tyr Pro Gl	Pro Ile 340	Gly Ala	Val Ile 345	Ser Pro	o Leu Le	Gly 350	Gly	Tyr	
aaa gat tt Lys Asp Ph 35	Lys Asp	tta ccc Leu Pro	tac gcc Tyr Ala 360	tgc tc Cys Se	t tta tg r Leu Cy 36	s Thr	gct Ala	tgt Cys	1104
gac aac gt Asp Asn Va 370									1152
cat cgt cg His Arg Ar 385	g gtg atg g Val Met	gct gaa Ala Glu 390	aaa ggg Lys Gly	atc ac Ile Th 39	r Ala Ly	a gca s Ala	gag Glu	caa Gln 400	1200
cgg gcg at Arg Ala Il	a aaa atg e Lys Met 405	Phe Ala	tat gcc Tyr Ala	aat ag Asn Se 410	t cat cc r His Pr	a gga o Gly	ttg Leu 415	tgg Trp	1248
aaa gtc gg Lys Val Gl	g atg atg y Met Met 420	gcc ggt Ala Gly	gct cat Ala His 425	Ala Al	a agc tg a Ser Tr	g ttt p Phe 430	atc Ile	aat Asn	1296
ggc ggc aa Gly Gly Ly 43	s Thr Pro	ctc aaa Leu Lys	ttt ggc Phe Gly 440	gcg at Ala Il	t agc ga e Ser As 44	p Trp	atg Met	gaa Glu	1344
gca cgc ga Ala Arg As 450	t ctt cct p Leu Pro	gaa gct Glu Ala 455	Asp Gly	gag ag Glu Se	t ttc cg r Phe Ar 460	t agt g Ser	tgg Trp	ttt Phe	1392
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aat ttg go Asn Leu Al				Lys Hi			Leu		96
ctg acg ga Leu Thr Gl	g aga gtt u Arg Val 5	tcc gta Ser Val	gtt ggt Val Gly 40	tta ag Leu Ar	g Asn Il	c agg e Arg 5	cgc Arg	agg Arg	144
aga aaa ag Arg Lys Ar	a atg gat g Met Asp	aat cga Asn Arg	ggc gaa Gly Glu	ttt tt Phe Le	g aat aa u Asn As	c gtt n Val	gct Ala	cag Gln	192

	50					55		-			60	÷				
gca Ala 65	ctg Leu	ggt Gly	cgc Arg	ccg Pro	ctg Leu 70	cga Arg	ctt Leu	gaa Glu	ccg Pro	caa Gln 75	gca Ala	gaa Glu	gat Asp	gcg Ala	ccg Pro 80	240
ctt Leu	aac Asn	aac Asn	tat Tyr	gct Ala 85	aac Asn	gag Glu	cgg Arg	ctt Leu	acc Thr 90	caa Gln	ctt Leu	aac Asn	caa Gln	cag Gln 95	cag Gln	288
cgc Arg	tgt Cys	gac Asp	gcg Ala 100	ttt Phe	att Ile	cag Gln	ttt Phe	gcc Ala 105	agc Ser	gat Asp	gtt Val	atg Met	ttg Leu 110	acg Thr	cgc Arg	336
tgt Cys	gag Glu	ctg Leu 115	acc Thr	agc Ser	gag Glu	gcg Ala	aag Lys 120	gcg Ala	gca Ala	gaa Glu	gct Ala	gca Ala 125	ata Ile	cgt Arg	ctg Leu	384
tgt Cys	aaa Lys 130	gag Glu	ctg Leu	gga Gly	gat Asp	cag Gln 135	tcg Ser	gtc Val	gtg Val	att Ile	agc Ser 140	ggt Gly	gac Asp	acg Thr	agg Arg	432
ctg Leu 145	gag Glu	gaa Glu	ttg Leu	ggg Gly	att Ile 150	agc Ser	gaa Glu	cgt Arg	ttg Leu	cag Gln 155	cag Gln	gaa Glu	tgc Cys	aat Asn	gcc Ala 160	480
gtt Val	gtt Val	tgg Trp	gat Asp	ccg Pro 165	gcg Ala	aaa Lys	ggt Gly	gcc Ala	gag Glu 170	aat Asn	atc Ile	tcg Ser	cag Gln	gca Ala 175	gag Glu	528
cag Gln	gct Ala	aaa Lys	gtg Val 180	ggt Gly	gtt <b>Val</b>	gtg Val	tat Tyr	gct Ala 185	gaa Glu	tat Tyr	ggt Gly	tta Leu	acc Thr 190	gaa Glu	tcg Ser	576
gga Gly	ggc Gly	gtg Val 195	gtt Val	ctt Leu	ttt Phe	tcc Ser	gcc Ala 200	gcc Ala	gag Glu	cgc Arg	Gly	cgt Arg 205	tca Ser	ttg Leu	agc Ser	624
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ccg Pro 225	cgt Arg	gta Val	gcg Ala	caa Gln	ctc Leu 230	gca Ala	gaa Glu	aaa Lys	ttg Leu	cat His 235	cag Gln	aaa Lys	gcg Ala	cag Gln	gcc Ala 240	720
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cca Pro	cag Gln 290	tac Tyr	aaa Lys	att Ile	gga Gly	aac Asn 295	att Ile	aat Asn	aaa Lys	tct Ser	gaa Glu 300	ctc Leu	aaa Lys	acg Thr	atg Met	912
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gaa Glu	aat Asn	cgt Arg	gaa Glu 100	gtt Val	gtc Val	gat Asp	acc Thr	tac Tyr 105	aaa Lys	ata Ile	ggg Gly	ata Ile	gat Asp 110	aaa Lys	gcc Ala	336	;
att Ile	gaa Glu	gct Ala 115	gca Ala	caa Gln	aaa Lys	tca Ser	acg Thr 120	ccg Pro	acg Thr	ctc Leu	ctt Leu	tca Ser 125	tta Leu	atg Met	gat Asp	384	
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Phe	Leu	Pro	Glu 180	Leu	Phe	Gln	Asn	His 185		Туг	Tyr	Thr	Ala 190	Ala	Val	576	5
ggt Gly	aaa Lys	tgg Trp 195	His	ttg Leu	tca Ser	aaa Lys	atc Ile 200	Ser	aat Asn	gtg Val	ccg Pro	gta Val 205	Pro	gaa Glu	gat Asp	624	l
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Pro His Asn P	cc aac ac ro Asn Th 485			_			-		1488
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gcc aat ccg c Ala Asn Pro G 530		_	_			_			1632
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cat cac gat His His Asp 130											432
gaa cat ggc Glu His Gly 145	gag tat Glu Tyr	cag gat Gln Asp 150	gcc c Ala H	cat gca His Ala	cga Arg 155	gcc Ala	cat His	gcc Ala	aat Asn	gac Asp 160	480
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tta ttt ggc Leu Phe Gly	tta acc Leu Thr 180	ggt ggc Gly Gly	Leu I	atc ccc Ile Pro 185	tgc Cys	ccg Pro	gca Ala	gca Ala 190	att Ile	acc Thr	576
gtg ctg ttg Val Leu Leu 195	ata tgc Ile Cys	att cag Ile Gln	ttg a Leu I 200	aaa gcc Lys Ala	ctg Leu	aca Thr	ctg Leu 205	ggc Gly	gca Ala	aca Thr	624
ctg gtc gtc Leu Val Val 210											672
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	-	_	_	_				-	-	-	acc Thr	_	-	-		240
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											cat His					336
											tac Tyr					384
											ggg Gly 140					432
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ctg cta gca a Leu Leu Ala I 545	att tct ata Ile Ser Ile 550	aaa ttc att Lys Phe Ile	cat tct tac His Ser Tyr 555	ttt aag aat Phe Lys Asn	gat 1680 Asp 560
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ggc aaa aga d Gly Lys Arg <i>l</i> 35	cga gta aga Arg Val Arg	att tca agt Ile Ser Ser 40	caa agc ctt Gln Ser Leu	aaa cgt gcg Lys Arg Ala 45	atg 144 Met
cgt aaa agt o Arg Lys Ser 0 50	ggt tat tac Gly Tyr Tyr	gca caa aat Ala Gln Asr 55	att ggt gaa 1 Ile Gly Glu 60	tcc agt ctc Ser Ser Leu	aga 192 Arg
acc att cat of Thr Ile His 1	ctt gca caa Leu Ala Gln 70	tta cgt gat Leu Arg Asp	gtt ctt cgg Val Leu Arg 75	caa aaa ctt Gln Lys Leu	ggt 240 Gly 80
gaa cgt ttt ( Glu Arg Phe )	gac caa aaa Asp Gln Lys 85	atc atc gat Ile Ile Asp	aag aca tta Lys Thr Leu 90	gcg ctg ctc Ala Leu Leu 95	tcc 288 Ser
Gly Lys Ser '	gtt gat gaa Val Asp Glu 100	gcc gaa aad Ala Glu Lys 10	g att tet gee s Ile Ser Ala s	gat gcg gtt Asp Ala Val 110	act 336 Thr
ccc tgg gtt o Pro Trp Val 1	gtg gga gaa Val Gly Glu	ata gcc tgc Ile Ala Tr <sub>1</sub> 120	g ttc tgt gag o Phe Cys Glu	cag gtt gca Gln Val Ala 125	aaa 384 Lys

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gaa Glu 145	gat Asp	att Ile	gcc Ala	gcc Ala	ata Ile 150	cgt Arg	gtg Val	aat Asn	tta Leu	cag Gln 155	cag Gln	ggt Gly	gtt Val	gat Asp	att Ile 160	480
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gtt Val	gat Asp	tct Ser 195	gat Asp	att Ile	gac Asp	tgg Trp	ttc Phe 200	acc Thr	gct Ala	gta Val	gat Asp	gat Asp 205	tta Leu	cag Gln	gaa Glu	624
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Arg Leu Pro His Val Pro Glu Gly His Lys Cys Gly Arg Leu His Gly
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cat tcc ttt atg gtg cga ctg gaa att acc ggg gaa gtc gat ccg cat
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His Ser Phe Met Val Arg Leu Glu Ile Thr Gly Glu Val Asp Pro His
acg ggc tgg att atc gat ttc gct gaa cta aaa gcg gcg ttt aaa cca
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Thr Gly Trp Ile Ile Asp Phe Ala Glu Leu Lys Ala Ala Phe Lys Pro
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Thr Tyr Glu Arg Leu Asp His His Tyr Leu Asn Asp Ile Pro Gly Leu
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                                                                     336
Lys Pro Val Val Pro Leu Leu Ser Ala Val Met Val Lys Glu Thr Cys .
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att att att ggt gcc ggt att gca ggc acc gct tgc gcg tta cgc
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Ile Ile Ile Gly Ala Gly Ile Ala Gly Thr Ala Cys Ala Leu Arg
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20 25 tgc gcg cga gcg ggt tta tcc gtt ttg tta ctg gaa cgc gct gaa atc 144 Cys Ala Arg Ala Gly Leu Ser Val Leu Leu Leu Glu Arg Ala Glu Ile 40 ccc ggc agc aaa aat ctt tcc ggc ggg cgg tta tat acc cat gca ctc 192 Pro Gly Ser Lys Asn Leu Ser Gly Gly Arg Leu Tyr Thr His Ala Leu geg gaa etc etc eeg caa ttt eat etg ace geg eet ett gaa ega ege 240 Ala Glu Leu Leu Pro Gln Phe His Leu Thr Ala Pro Leu Glu Arg Arg atc act cac gaa agc ctt tcc ctg tta acg ccc gat ggc gta acg acg 288 Ile Thr His Glu Ser Leu Ser Leu Leu Thr Pro Asp Gly Val Thr Thr 336 ttt tcc agc tta cag ccc ggc ggt gaa tcc tgg agt gta tta cgt gca Phe Ser Ser Leu Gln Pro Gly Gly Glu Ser Trp Ser Val Leu Arg Ala cga ttc gat ccg tgg ctg gtt gcc gaa gcc gaa aaa gaa ggt gtc gaa 384 Arg Phe Asp Pro Trp Leu Val Ala Glu Ala Glu Lys Glu Gly Val Glu 120 432 tgc atc ccc gga gcg acg gtg gat gca ctg tat gaa gaa aac ggc aga Cys Ile Pro Gly Ala Thr Val Asp Ala Leu Tyr Glu Glu Asn Gly Arg 135 gtc tgt ggc gtt att tgt ggt gac gat att ctc cgc gcc cgt tat gtg 480 Val Cys Gly Val Ile Cys Gly Asp Asp Ile Leu Arg Ala Arg Tyr Val 150 155 gtg ctg gca gaa ggt gcc aac agc gtc ctg gct gaa cgt cac ggg tta 528 Val Leu Ala Glu Gly Ala Asn Ser Val Leu Ala Glu Arg His Gly Leu 165 qtq act cqt cct qct qgc gaa gcg atg gcg ttg ggg atc aaa gaa gtg 576 Val Thr Arg Pro Ala Gly Glu Ala Met Ala Leu Gly Ile Lys Glu Val 185 180 ctg tcg ctg gaa aca tcc gct att gaa gaa cgt ttt cat ctg gag aat 624 Leu Ser Leu Glu Thr Ser Ala Ile Glu Glu Arg Phe His Leu Glu Asn 200 205 aac gaa ggc gca gcg ttg ctg ttc agc ggc agg atc tgt gat gac tta 672 Asn Glu Gly Ala Ala Leu Leu Phe Ser Gly Arg Ile Cys Asp Asp Leu 210 215 ccc ggc ggc gca ttt ctt tat act aat caa caa acg ctc tcg tta ggg 720 Pro Gly Gly Ala Phe Leu Tyr Thr Asn Gln Gln Thr Leu Ser Leu Gly 235 240 225 768 att gtt tgc ccg ctc tct tcc ctt acg caa agt cgt gtt ccg gca agc Ile Val Cys Pro Leu Ser Ser Leu Thr Gln Ser Arg Val Pro Ala Ser 245 gag ctg ctg act cgc ttt aaa gcg cat ccg qca gtg cgc ccg ctt atc Glu Leu Leu Thr Arg Phe Lys Ala His Pro Ala Val Arg Pro Leu Ile

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cta aaa Leu Lys	gat ggc Asp Gly	ggc aaa Gly Lys	ggt Gly	att Ile	aaa Lys	atc Ile	gat Asp	gaa Glu	gtt Val	gtc Val	aaa Lys	gga Gly	1200

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	act Thr															144
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ccg Pro	tac Tyr	aac Asn	ctc Leu	ggg Gly 165	cag Gln	acc Thr	att Ile	acc Thr	cag Gln 170	ggg Gly	att Ile	att Ile	agt Ser	gcc Ala 175	acg Thr	528
ggt Gly	cga Arg	atc Ile	ggt Gly 180	ctg Leu	aac Asn	ccg Pro	acc Thr	ggg Gly 185	cgg Arg	caa Gln	aac Asn	ttc Phe	ctc Leu 190	caa Gln	acc Thr	576
gat Asp	gct Ala	tcc Ser 195	att Ile	aac Asn	cac His	ggt Gly	aac Asn 200	tct Ser	ggc Gly	ggc Gly	gcg Ala	ctg Leu 205	gtg Val	aac Asn	tcg Ser	624
ctg Leu	ggc Gly 210	gaa Glu	ctg Leu	atg Met	ggc Gly	att Ile 215	aat Asn	acg Thr	ctg Leu	tcg Ser	ttt Phe 220	gat Asp	aag Lys	agt Ser	aac Asn	672
gat Asp 225	ggc Gly	gaa Glu	acg Thr	ccg Pro	gaa Glu 230	ggt Gly	atc Ile	ggc Gly	ttt Phe	gcg Ala 235	att Ile	cct Pro	ttc Phe	cag Gln	tta Leu 240	720
gca Ala	acc Thr	aaa Lys	att Ile	atg Met 245	gat Asp	aag Lys	ctg Leu	atc Ile	cgc Arg 250	gat Asp	ggt Gly	cgc Arg	gtg Val	atc Ile 255	cgc Arg	768
ggc Gly	tac Tyr	att Ile	ggt Gly 260	atc Ile	ggc Gly	gga Gly	cgt Arg	gag Glu 265	atc Ile	gca Ala	cca Pro	ctg Leu	cac His 270	gcg Ala	cag Gln	816
ggc Gly	ggt Gly	ggt Gly 275	ata Ile	gat Asp	caa Gln	ctg Leu	caa Gln 280	GJA aaa	atc Ile	gtg Val	gtt Val	aat Asn 285	gaa Glu	gtg Val	tca Ser	864
cct Pro	gac Asp 290	ggc	ccg Pro	gcg Ala	gcg Ala	aat Asn 295	gcg Ala	ggt Gly	att Ile	cag Gln	gtc Val 300	Asn	gat Asp	ctg Leu	att Ile	912
att Ile 305	Ser	gtg Val	gat Asp	aac Asn	aaa Lys 310	ccg Pro	gcc Ala	atc Ile	tct Ser	gct Ala 315	Leu	gag Glu	acg Thr	atg Met	gat Asp 320	960
cag Gln	gtg Val	gcg Ala	gaa Glu	att Ile 325	cgc Arg	cct Pro	ggt Gly	tcg Ser	gtg Val 330	Ile	cct Pro	gta Val	gta Val	gtg Val 335	atg Met	1008
cgt Arg	gat Asp	gat Asp	aag Lys 340	Gln	tta Leu	acg Thr	ctg Leu	cag Gln 345	Val	acc Thr	att	cag Gln	gaa Glu 350	Tyr	ccg Pro	1056
-	acc Thr															1068

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atc ctg gct gca gcg g Ile Leu Ala Ala Ala G 35	ggt atc gct gaa Gly Ile Ala Glu 40	gat gtt aag atc Asp Val Lys Ile 45	agt gag ctg 144 Ser Glu Leu
tct gaa gga caa atc g Ser Glu Gly Gln Ile A 50			
gtt gaa ggt gat ctg c Val Glu Gly Asp Leu A 65			
atg gat ctt ggt tgc t Met Asp Leu Gly Cys T 85	tat cgc ggt ttg Tyr Arg Gly Leu	cgt cat cgt cgt Arg His Arg Arg 90	ggt ctc ccg 288 Gly Leu Pro 95
gtt cgc ggt cag cgt a Val Arg Gly Gln Arg T 100			
cgc aaa ccg atc aag a Arg Lys Pro Ile Lys I 115			357
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	Asp	Gly	Val 20	Ala	His	Ile	His	Ala 25	Ser	Phe	Asn	Asn	Thr 30	Ile	Val	
act Thr	atc Ile	act Thr 35	gat Asp	cgt Arg	cag Gln	ggt Gly	aac Asn 40	gcg Ala	ttg Leu	ggt Gly	tgg Trp	gca Ala 45	aca Thr	gcc Ala	ggt Gly	144
ggt Gly	tcc Ser 50	ggt Gly	ttc Phe	cgt Arg	ggt Gly	tct Ser 55	cgc Arg	aaa Lys	tcc Ser	act Thr	ccg Pro 60	ttt Phe	gca Ala	gct Ala	cag Gln	192
gtt Val 65	gca Ala	gca Ala	gag Glu	cgt Arg	tgc Cys 70	gct Ala	gac Asp	gcc Ala	gtg Val	aaa Lys 75	gaa Glu	tac Tyr	ggc Gly	atc Ile	aag Lys 80	240
aat Asn	ctg Leu	gaa Glu	gtt Val	atg Met 85	gtt Val	aaa Lys	ggt Gly	ccg Pro	ggt Gly 90	cca Pro	ggc Gly	cgc Arg	gaa Glu	tct Ser 95	act Thr	288
att Ile	cgt Arg	gct Ala	ctg Leu 100	aac Asn	gcc Ala	gca Ala	ggt <sup>°</sup> Gly	ttc Phe 105	cgc Arg	atc Ile	act Thr	aac Asn	att Ile 110	act Thr	gat Asp	336
gtg Val	act Thr	ccg Pro 115	atc Ile	cct Pro	cat His	aac Asn	ggt Gly 120	tgt Cys	cgt Arg	ccg Pro	ccg Pro	aaa Lys 125	aaa Lys	cgt Arg	cgc Arg	384
gta Val	taa *															390
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<21: <21: <22: <22: <22: <40: atg Met 1 acc Thr	1> 6: 2> D1 3> E: 1> C1 2> (: 0> 2- 9ca Ala gac Asp	21 NA scher DS 1) 49 aga Arg	tat Tyr ttc Phe 20	ttg Leu 5 ctt Leu	ggt Gly aag Lys cct	Pro tct Ser	Lys ggc Gly cag	gtt Val 25	Lys 10 cgc Arg	gcg Ala	Ser atc Ile	gat Asp	acc Thr 30	Glu 15 aag Lys cgt	tgt Cys ctg	
<21: <21: <22: <22: <22: <40: atg Met 1 acc Thr	l> 6: 2> DI 3> E: 1> CI 2> (: 0> 2 gca Ala gac Asp att Ile	21 NA scher DS 1) 49 aga Arg tta Leu gaa Glu 35 tat	tat Tyr ttc Phe 20 caa Gln	ttg Leu 5 ctt Leu gct Ala	ggt Gly aag Lys cct Pro	tct ser ggc Gly	ggc Gly cag Gln 40	gtt Val 25 cac His	Lys 10 cgc Arg ggt Gly	gcg Ala gcg Ala	atc Ile cgt Arg	gat Asp aaa Lys 45 gtt Val	acc Thr 30 ccg Pro	Glu 15 aag Lys cgt Arg	tgt Cys ctg Leu	96

65					70					75					80	
_	ctg Leu						_		-	_	-	-	-	-		288
_	ctg Leu	_		-	_		-	_				_		_	-	336
	gca Ala															384
	gtt Val 130															432
	cgt Arg															480
	gct Ala															528
_	atg Met	-		_		-	-	-	_		-		_	_		576
	gac Asp			_		_		_					_	taa *		621
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	)> L> CI 2> (1		. (99	0)												
atg	)> 25 cag Gln	ggt								-	_	_	_	-		48
	caa Gln															96
	ggc Gly															144
	tcg Ser 50															192

cta Leu 65	cat His	gag Glu	tac Tyr	agc Ser	acc Thr 70	aaa Lys	gaa Glu	ggc Gly	gtt Val	cag Gln 75	gaa Glu	gat Asp	atc Ile	ctg Leu	gaa Glu 80	2	40
atc Ile	ctg Leu	ctc Leu	aac Asn	ctg Leu 85	aaa Lys	ggg Gly	ctg Leu	gcg Ala	gtg Val 90	aga Arg	gtt Val	cag Gln	ggc Gly	aaa Lys 95	gat Asp	2	88
gaa Glu	gtt Val	att Ile	ctt Leu 100	acc Thr	ttg Leu	aat Asn	aaa Lys	tct Ser 105	ggc Gly	att Ile	ggc Gly	cct Pro	gtg Val 110	act Thr	gca Ala	3	336
					gac Asp											3	384
gtg Val	atc Ile 130	tgc Cys	cac His	ctg Leu	acc Thr	gat Asp 135	gag Glu	aac Asn	gcg Ala	tct Ser	att Ile 140	agc Ser	atg Met	cgt Arg	atc Ile	4	132
aaa Lys 145	gtt Val	cag Gln	cgc Arg	ggt Gly	cgt Arg 150	ggt Gly	tat Tyr	gtg Val	ccg Pro	gct Ala 155	tct Ser	acc Thr	cga Arg	att Ile	cat His 160	4	180
tcg Ser	gaa Glu	gaa Glu	gat Asp	gag Glu 165	cgc Arg	cca Pro	atc Ile	ggc Gly	cgt Arg 170	ctg Leu	ctg Leu	gtc Val	gac Asp	gca Ala 175	tgc Cys	5	528
tac Tyr	agc Ser	cct Pro	gtg Val 180	gag Glu	cgt Arg	att Ile	gcc Ala	tac Tyr 185	aat Asn	gtt Val	gaa Glu	gca Ala	gcg Ala 190	cgt Arg	gta Val	5	576
gaa Glu	cag Gln	cgt Arg 195	acc Thr	gac Asp	ctg Leu	gac Asp	aag Lys 200	ctg Leu	gtc Val	atc Ile	gaa Glu	atg Met 205	gaa Glu	acc Thr	aac Asn	e	624
ggc Gly	aca Thr 210	atc Ile	gat Asp	cct Pro	gaa Glu	gag Glu 215	gcg Ala	att Ile	cgt Arg	cgt Arg	gcg Ala 220	gca Ala	acc Thr	att Ile	ctg Leu	•	672
gct Ala 225	gaa Glu	caa Gln	ctg Leu	gaa Glu	gct Ala 230	ttc Phe	gtt Val	gac Asp	tta Leu	cgt Arg 235	gat Asp	gta Val	cgt Arg	cag Gln	cct Pro 240	Ī	720
gaa Glu	gtg Val	aaa Lys	gaa Glu	gag Glu 245	aaa Lys	cca Pro	gag Glu	ttc Phe	gat Asp 250	ccg Pro	atc Ile	ctg Leu	ctg Leu	cgc Arg 255	cct Pro	•	768
gtt Val	gac Asp	gat Asp	ctg Leu 260	gaa Glu	ttg Leu	act Thr	gtc Val	cgc Arg 265	tct Ser	gct Ala	aac Asn	tgc Cys	ctt Leu 270	aaa Lys	gca Ala	8	816
					atc Ile			Leu								{	864
		Lys			aac Asn		Gly					Thr					912

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tgg cca ccg c Trp Pro Pro A					990
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atc atc aag a Ile Ile Lys 3 35	-				•
gag ccg ctg a Glu Pro Leu 1 50		-		_	-
ctg gca ttc g Leu Ala Phe A 65					
aac gaa ctg ( Asn Glu Leu (					_
att ctg aag t Ile Leu Lys (			Asp Asn Ala		
atc gag ctg ( Ile Glu Leu V 115					taa 384 *
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ggc ttc cgt gct cgt atg gct act aaa aat ggt cgt cag gtt ctg gca Gly Phe Arg Ala Arg Met Ala Thr Lys Asn Gly Arg Gln Val Leu Ala 20 25 30	96
cgt cgt cgt gct aaa ggc cgc gct cgt ctg acc gtt tct aag taa Arg Arg Arg Ala Lys Gly Arg Ala Arg Leu Thr Val Ser Lys * 35 40 45	141
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caa ttc aca ttc gtc ttc cag cag cca caa cgg gct ggc acg ccg caa Gln Phe Thr Phe Val Phe Gln Gln Pro Gln Arg Ala Gly Thr Pro Gln 20 25 30	96
att acc att ctc ggc cgc ctg aat tcg ctg ggg cat ccc cgt atc ggt Ile Thr Ile Leu Gly Arg Leu Asn Ser Leu Gly His Pro Arg Ile Gly 35 40 45	144
ctt aca gtc gcc aag aaa aac gtt cga cgc gcc cat gaa cgc aat cgg Leu Thr Val Ala Lys Lys Asn Val Arg Arg Ala His Glu Arg Asn Arg 50 55 60	192
att aaa cgt ctg acg cgt gaa agc ttc cgt ctg cgc caa cat gaa ctc Ile Lys Arg Leu Thr Arg Glu Ser Phe Arg Leu Arg Gln His Glu Leu 65 70 75 80	240
ccg gct atg gat ttc gtg gtg gtg gcg aaa aaa ggg gtt gcc gac ctc Pro Ala Met Asp Phe Val Val Val Ala Lys Lys Gly Val Ala Asp Leu 85 90 95	288
gat aac cgt gct ctc tcg gaa gcg ttg gaa aaa tta tgg cgc cgc cac Asp Asn Arg Ala Leu Ser Glu Ala Leu Glu Lys Leu Trp Arg Arg His 100 105 110	336
tgt cgc ctg gct cgc ggg tcc tga Cys Arg Leu Ala Arg Gly Ser * 115	360

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gac tct cgt gcc gaa acc caa gag cgc gtg atg gac tcc aac gat ttg Asp Ser Arg Ala Glu Thr Gln Glu Arg Val Met Asp Ser Asn Asp Leu 35 40 45	144
gag aaa gag cgt ggg att acc atc ctc gcg aaa aac acc gct atc aaa Glu Lys Glu Arg Gly Ile Thr Ile Leu Ala Lys Asn Thr Ala Ile Lys 50 55 60	192
tgg aat gat tac cgt atc aac atc gtt gat acc ccg ggg cac gcc gac Trp Asn Asp Tyr Arg Ile Asn Ile Val Asp Thr Pro Gly His Ala Asp 65 70 75 80	240
ttc ggt ggt gaa gtt gaa cgt gta atg tcc atg gta gac tca gtg ctg Phe Gly Gly Glu Val Glu Arg Val Met Ser Met Val Asp Ser Val Leu 85 90 95	288
ctg gtg gtt gac gca ttt gac ggc ccg atg ccg caa acg cgc ttc gta Leu Val Val Asp Ala Phe Asp Gly Pro Met Pro Gln Thr Arg Phe Val 100 105 110	336
acc aaa aaa gcg ttt gct tac ggc ctg aag ccg att gtt gtt atc aac Thr Lys Lys Ala Phe Ala Tyr Gly Leu Lys Pro Ile Val Val Ile Asn 115 120 125	384
aaa gtt gac cgc cct ggc gcg cgt cct gat tgg gtt gtg gat cag gta Lys Val Asp Arg Pro Gly Ala Arg Pro Asp Trp Val Val Asp Gln Val 130 135 140	432
ttc gat ctg ttc gtt aac ctc gac gcg acc gac gag cag ctg gac ttc Phe Asp Leu Phe Val Asn Leu Asp Ala Thr Asp Glu Gln Leu Asp Phe 145 150 155 160	480
ccg atc gtt tac gct tct gcg ctg aac ggt atc gcg ggt ctg gac cac Pro Ile Val Tyr Ala Ser Ala Leu Asn Gly Ile Ala Gly Leu Asp His 165 170 175	528
gaa gat atg gcg gaa gac atg acc ccg ctg tac cag gcg att gtt gac Glu Asp Met Ala Glu Asp Met Thr Pro Leu Tyr Gln Ala Ile Val Asp 180 185 190	576
cac gtt cct gcg ccg gac gtt gac ctt gac ggt ccg ttc cag atg cag His Val Pro Ala Pro Asp Val Asp Leu Asp Gly Pro Phe Gln Met Gln 195 200 205	624

					tac Tyr											672
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gat Asp	agc Ser	gaa Glu	ggc Gly	aaa Lys 245	acc Thr	cgc Arg	aac Asn	gcg Ala	aaa Lys 250	gtc Val	ggt Gly	aaa Lys	gtg Val	ctg Leu 255	ggc Gly	768
					cgt Arg											816
	_			-	ggc Gly			_	_				-		_	864
					gtt Val											912
					ttc Phe 310											960
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aaa Lys	gaa Glu	ctg Leu	gta Val 340	cac His	aac Asn	gtt Val	gcg Ala	ctg Leu 345	cgc Arg	gta Val	gaa Glu	gaa Glu	acc Thr 350	gaa Glu	gac Asp	1056
					gtt Val											1104
					cgt Arg											1152
					cgt Arg 390											1200
gaa Glu	aac Asn	gtg Val	act Thr	ctg Leu 405	gac Asp	gtt Val	gaa Glu	gaa Glu	cag Gln 410	cat His	cag Gln	ggt Gly	tct Ser	gta Val 415	atg Met	1248
cag Gln	gcg Ala	ctg Leu	ggc Gly 420	gaa Glu	cgt Arg	aaa Lys	ggc Gly	gac Asp 425	ctg Leu	aaa Lys	aac Asn	atg Met	aat Asn 430	cca Pro	gac Asp	1296
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ggt cac ggt gca ga Gly His Gly Ala Gl 515		Gly Gln Ile 1	
cgc tct aac gac ct Arg Ser Asn Asp Le 530	-	Cys Leu Thr (	
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			aac Asn	-	-		-	_	-	_		_			_		192
			gac Asp														240
			caa Gln														288
			gcc Ala 100														336
			att Ile														384
			atg Met														432 
			atg Met														480
			cag Gln														528
			gac Asp 180														576
atc Ile	gaa Glu	cga Arg 195	act Thr	tcc Ser	ctc Leu	ggt Gly	tct Ser 200	ttg Leu	ctt Leu	gac Asp	cat His	act Thr 205	ggc Gly	gca Ala	ttt Phe		624
ggc Gly	gaa Glu 210	agc Ser	gaa Glu	aaa Lys	tat Tyr	gcc Ala 215	gca Ala	cgc Arg	gta Val	ttt Phe	ggt Gly 220	gcc Ala	gat Asp	cgc Arg	tcc Ser		672
tgg Trp 225	tcg Ser	gta Val	gtc Val	gtc Val	ggt Gly 230	act Thr	tcc Ser	ggc Gly	tct Ser	aac Asn 235	cgc Arg	acc Thr	atc Ile	atg Met	cag Gln 240		720
			acc Thr														768
			gaa Glu 260													•	816
atg Met	gtg Val	cca Pro 275	agc Ser	cgc Arg	aac Asn	cgc Arg	tac Tyr 280	ggc Gly	att Ile	atc Ile	ggg Gly	cca Pro 285	atc Ile	tat Tyr	ccg Pro		864

	gaa Glu 290															912
	acc Thr															960
	tgc Cys															1008
	ctg Leu															1056
	tat Tyr	_	_			_			_	_			-	-	-	1104
	gaa Glu 370			-						_		-				1152
	cac His															1200
	gaa Glu															1248
	atg Met															1296
-	gtg Val			_	-	_	_			_		_		_		1344
_	gaa Glu 450			-	-		-	_		_	_	_	_			1392
	tat Tyr															1440
	aaa Lys															1488
	gac Asp															1536
_	cat His	_		_	-						-		_	_		1584

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					ctg Leu 550											1680
					cgc Arg											1728
			_		ctg Leu			_		_		-				1776
					acc Thr											1824
					cag Gln											1872
					atg Met 630											1920 .
					aac Asn											1968
					gcg Ala											2016
					gtc Val											2064
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tat Tyr	tta Leu	cgc Arg	tcg Ser	ctg Leu 725	caa Gln	tcc Ser	tgg Trp	gac. Asp	cac His 730	cat His	ttc Phe	cct Pro	gga Gly	ttt Phe 735	gaa Glu	2208
cac His	gaa Glu	act Thr	gaa Glu 740	Gly	act Thr	gaa Glu	att Ile	att Ile 745	gac Asp	ggt Gly	att Ile	tac Tyr	cac His 750	gtt Val	atg Met	2256
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aac cat atg gcg tta tta aat tgt gaa aat aat att atc gac gtc Asn His Met Ala Leu Leu Asn Cys Glu Asn Asn Ile Ile Asp Val 35 40 45	
tct ctt aac aac act ttg gtt gct cat att agt cac gac atc atc Ser Leu Asn Asn Thr Leu Val Ala His Ile Ser His Asp Ile Ile 50 55 60	
gat tac ctc cgg ttt ctg aat aaa gat ctc tcg caa ata cca gta Asp Tyr Leu Arg Phe Leu Asn Lys Asp Leu Ser Gln Ile Pro Val 65 70 75	
caa cgt agc gct acg ccc ata ctc acc ctg cca tgc ctg acg cca Gln Arg Ser Ala Thr Pro Ile Leu Thr Leu Pro Cys Leu Thr Pro 85 90 95	
gtc ttt cgc gtt gcc gcg caa cac agc atg atg ccc gca gaa act Val Phe Arg Val Ala Ala Gln His Ser Met Met Pro Ala Glu Thr 100 105 110	
tca gaa aag gaa cga aca cgc gca tta tta ttc acg gtg cta tcc Ser Glu Lys Glu Arg Thr Arg Ala Leu Leu Phe Thr Val Leu Ser 115 120 125	_
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agt ctg tta aag aaa aag ttg aaa agc gaa aac acc agt tat agc Ser Leu Leu Lys Lys Lys Leu Lys Ser Glu Asn Thr Ser Tyr Ser 180 185 190	
ata atc acc acc tgc cgc atg cgt tat gcc gta aat gaa tta atg	atg 624

Ile Ile Thr Thr C		Arg Tyr Ala Val 200	Asn Glu Leu Met 205	Met
gac ggt aaa aat a Asp Gly Lys Asn I 210	c tct cag g e Ser Gln V 215	/al Ser Gln Ser	tgc ggc tac aac Cys Gly Tyr Asn 220	agt 672 Ser
acg tcg tac ttt at Thr Ser Tyr Phe I 225	t tot gto to e Ser Val Pi 230	tt aaa gac ttc Phe Lys Asp Phe 235	tac ggt atg acg Tyr Gly Met Thr	ccg 720 Pro 240
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ttt gat ttt atg a Phe Asp Phe Met M 50				
ctt ggc att acg g Leu Gly Ile Thr A 65				
ata gcc aga cct a Ile Ala Arg Pro I				
tat ggt cgt aag c Tyr Gly Arg Lys P 100	ca atg atg a co Met Met M	atg tgg gca att Met Trp Ala Ile 105	ttc att tac tca Phe Ile Tyr Ser 110	gtc 336 Val
gga aca ggc ctt a Gly Thr Gly Leu S 115	er Gly Ile A	gct aca aac tta Ala Thr Asn Leu 120 .	tat atg ctc gca Tyr Met Leu Ala 125	gtt 384 Val
tgc cgt ttt att g Cys Arg Phe Ile V				

	130					135					140				
				gta Val	-	_								_	480
				gta Val 165											528
				cag Gln											576
			_	tta Leu		_			_				_	-	624
-		-	-	cag Gln				-	-			_	-		672
				gtc Val											720
_			-	tgt Cys 245		_				-			_		768
				tcc Ser		-	_	_			_			 -	816
			_	atg Met			_					_			864
				ttt Phe											912
				ata Ile											960
				aac Asn 325							_				1008
				tta Leu											1056
_				aca Thr			-								1104
			_	act Thr			_	-	_		-		-		1152

370	375		380	
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ttg cag tgt atc a Leu Gln Cys Ile A 50	•			
tta gtc gat tgc g Leu Val Asp Cys V 65	al Ile Val Ala		Tyr Leu His Lys	Glu
cca gta att aaa g Pro Val Ile Lys A				Lys
cca att gca tta a Pro Ile Ala Leu S 100				-
aaa gaa gct ggt g Lys Glu Ala Gly V 115		Ala Gly His	_	
aat ggg gtt caa t Asn Gly Val Gln T 130				

-				-			_	aga Arg				-				480
, ,	_						_	aaa Lys	_							528
							-	tgt Cys 185	_	_					-	576
			-	_		_		ggt Gly			_	_				624
					_	-	_	atg Met			_		_	-		672
								gag Glu								720
-	-			•				gga Gly								768
_	_		_		_			ctt Leu 265					-		_	816
		_	_		_			gaa Glu	-	-	-	-	-			864
		-			_	_	-	ggc Gly	_		_					912
								gcc Ala	_			_	_		_	960
							_	ggt Gly	_			-	_	_		1008
								gcc Ala 345								1056
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WO 01/34810 PCT/US00/30950.

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										atc Ile					144
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		-		_	-	Gln				gaa Glu	-		-		240
										aaa Lys					288
				_	_	-			_	tgc Cys		-		_	336
										cat His					384
										gct Ala 140					432
			_	-	_	_		_	-	aat Asn					480
										ctc Leu		Thr			528
	_	-	_	_			_	_		 caa Gln					576

					caa Gln											624
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					aac Asn											912
					caa Gln 310											960
	-	_	_		acc Thr			-			-					1008
					tca Ser											1056
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_	_				cca Pro	_		-		_	_		_	_	_	1152
					gcc Ala 390											1200
aac Asn	gcc Ala	tta Leu	gcc Ala	cgc Arg 405	gtc Val	aac Asn	aac Asn	ctg Leu	acg Thr 410	caa Gln	tcc Ser	atc Ile	ctg Leu	gca Ala 415	aaa Lys	1248
					ctt Leu											1296

ttg atc agc gga gaa aac agc gcc gcc gcg ttg ctg gaa aaa atc aaa Leu Ile Ser Gly Glu Asn Ser Ala Ala Ala Leu Leu Glu Lys Ile Lys 435 440 445	1344
gct gaa cgc gca gct agc ggg ggt aaa aaa gcc tca cgt aaa aaa tcc Ala Glu Arg Ala Ala Ser Gly Gly Lys Lys Ala Ser Arg Lys Lys Ser 450 455 460	1392
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ctg cgc gat ggc ggc gtt tcc tat caa aac tac gtc aat gaa ctc gcc Leu Arg Asp Gly Gly Val Ser Tyr Gln Asn Tyr Val Asn Glu Leu Ala 20 25 30	96
tcg ctg ctg ttt ttg aaa atg tgt aaa gag acc ggt cag gaa gcg gaa Ser Leu Leu Phe Leu Lys Met Cys Lys Glu Thr Gly Gln Glu Ala Glu 35 40 45	144
tac ctg ccg gaa ggt tac cgc tgg gat gac ctg aaa tcc cgc atc ggc Tyr Leu Pro Glu Gly Tyr Arg Trp Asp Asp Leu Lys Ser Arg Ile Gly 50 55 60	192
cag gag cag ttg cag ttc tac cga aaa atg ctc gtg cat tta ggc gaa Gln Glu Gln Leu Gln Phe Tyr Arg Lys Met Leu Val His Leu Gly Glu 65 70 75 80	240
gat gac aaa aag ctg gta cag gca gtt ttt cat aat gtt agt acc acc Asp Asp Lys Lys Leu Val Gln Ala Val Phe His Asn Val Ser Thr Thr 85 90 95	288
atc acc gag ccg aaa caa ata acc gca ctg gtc agc aat atg gat tcg Ile Thr Glu Pro Lys Gln Ile Thr Ala Leu Val Ser Asn Met Asp Ser 100 105 110	336
ctg gac tgg tac aac ggc gcg cac ggt aag tcg cgc gat gac ttc ggc Leu Asp Trp Tyr Asn Gly Ala His Gly Lys Ser Arg Asp Asp Phe Gly 115 120 125	384
gat atg tac gaa ggg ctg ttg cag aag aac gcg aat gaa acc aag tct Asp Met Tyr Glu Gly Leu Leu Gln Lys Asn Ala Asn Glu Thr Lys Ser 130 135 140	432
ggt gca ggc cag tac ttc acc ccg cgt ccg ctg att aaa acc att att	480

Gly 145	Ala	Gly	Gln	Tyr	Phe 150	Thr	Pro	Arg	Pro	Leu 155	Ile	Lys	Thr	Ile	Ile 160	
	ctg Leu															528
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	aat Asn															624
	cgc Arg 210															672
	ctg Leu															720
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	ccg Pro															816
	ggc Gly															864
	ttg Leu 290															912
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ggc Gly	acc Thr	gac Asp	att Ile	cgt Arg 325	cgt Arg	gac Asp	ctg Leu	atg Met	gat Asp 330	aag Lys	tgt Cys	cat His	ctg Leu	cac His 335	acc Thr	1008
	ctg Leu	_	_	_						_	_			_		1056
	gtg Val															1104
	aac Asn 370															1152
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Pro 385	Ser	Phe	Gly	Lys	Arg 390	Thr	Pro	Phe	Thr	Asp 395	Glu	His	Leu	Gln	Pro 400	-	
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_		_		-	ttt Phe		-	-		_	-	_	-	-	_		1296
					acc Thr											-	1344
					tgg Trp												1392
					gat Asp 470												1440
gag Glu	ccg Pro	gat Asp	gta Val	tta Leu 485	gcg Ala	gca Ala	gaa Glu	gcg Ala	atg Met 490	ggc Gly	gaa Glu	ctg Leu	gta Val	cag Gln 495	gcg Ala		1488
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ggg Gly	caa Gln	tca Ser	gca Ala 20	atg Met	gct Ala	agg Arg	ctt Leu	tta Leu 25	ggt Gly	gta Val	tca Ser	cct Pro	cca Pro 30	agc Ser	gta Val		96
aat Asn	caa Gln	tgg Trp	atc Ile	aaa Lys	Gly ggg	gta Val	cgt <sub>.</sub> Arg	caa Gln	ttg Leu	cct Pro	gcc Ala	gag Glu	aga Arg	tgt Cys	cca Pro		144

35 40 45 gca att gaa cgt gca aca aga ggt gag gtt ctg tgc gaa gaa ctt cgt 192 Ala Ile Glu Arg Ala Thr Arg Gly Glu Val Leu Cys Glu Glu Leu Arg cct gat att gac tgg tca tat tta cga cgt tcg gca tgt tgt tcg cag 240 Pro Asp Ile Asp Trp Ser Tyr Leu Arg Arg Ser Ala Cys Cys Ser Gln aat atg tca gtg aag caa cta aat gac agt aac aaa tcc tca ttt gat 288 Asn Met Ser Val Lys Gln Leu Asn Asp Ser Asn Lys Ser Ser Phe Asp 297 cat acc tga His Thr <210> 262 <211> 423 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(423) <400> 262 atg aaa atc aag cat gag cac atc gaa tca gtg ttg ttt gcc cta gca 48 Met Lys Ile Lys His Glu His Ile Glu Ser Val Leu Phe Ala Leu Ala 10 gcc gaa aaa ggg cag gca tgg gta gcc aat gca att act gaa gaa tat 96 Ala Glu Lys Gly Gln Ala Trp Val Ala Asn Ala Ile Thr Glu Glu Tyr ctg cgc cag ggg ggc ggc gaa ttg ccc ctg gtt cca ggc aag gac tgg 144 Leu Arg Gln Gly Gly Glu Leu Pro Leu Val Pro Gly Lys Asp Trp 192 aac aat cag cag aat atc tat cac cgt tgg ttg aaa ggt gaa acg aaa Asn Asn Gln Gln Asn Ile Tyr His Arg Trp Leu Lys Gly Glu Thr Lys acq caa aga gaa aaa att cag aag ctg atc cca gca att ctg gca atc 240 Thr Gln Arg Glu Lys Ile Gln Lys Leu Ile Pro Ala Ile Leu Ala Ile ctt ccg cgc gag ctg cgt cac cga ctc tgc atc ttc gat acc ctg gaa 288 Leu Pro Arg Glu Leu Arg His Arg Leu Cys Ile Phe Asp Thr Leu Glu cgc cgt gca tta ctg gcg gcg cag gaa gcg tta agt acg gca att gat 336 Arg Arg Ala Leu Leu Ala Ala Gln Glu Ala Leu Ser Thr Ala Ile Asp 105 geg cat gat gat gca gtc caa gcc gtt tac egg aaa gcg cat ttc agc 384 Ala His Asp Asp Ala Val Gln Ala Val Tyr Arg Lys Ala His Phe Ser 120

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	• •		cga tgg gct gat Arg Trp Ala Asp 75	
			ggc gag gaa tgg Gly Glu Glu Trp	
			agg gaa aaa tta Arg Glu Lys Leu 110	
			gcc aga aga agc Ala Arg Arg Ser 125	
gaa gca gat gtt Glu Ala Asp Val 130	caa aca aaa Gln Thr Lys 135	Gln Glu Arg	aat tta aca ggt Asn Leu Thr Gly 140	gtt caa 432 Val Gln
			gtc aac aca aag Val Asn Thr Lys 155	
			gat ccc ccc cta Asp Pro Pro Leu	

ccc cgg ggg Pro Arg Gly	_	-		_	-		_	-			576
ttg ccg aac Leu Pro Asn 195											624
cgc cag gca Arg Gln Ala 210		Lys P									672
gcg ata cgg Ala Ile Arg 225											720
cag gtg att Gln Val Ile	_	-	_	Asn (	-	-		_			768
ccg aaa ggt Pro Lys Gly											816
tcg tta ccg Ser Leu Pro 275	-		-	_				taa *			858
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ggg aag aac o Gly Lys Asn H 115	cac tta gco His Leu Ala	gca gct Ala Ala 120	atc ggg Ile Gly	aat cgc Asn Arg	ctg ctg Leu Leu 125	aaa gac Lys Asp	384
ggt cag aca g Gly Gln Thr V 130	gtg att gto Val Ile Val	gtt acc Val Thr 135	gtg gct Val Ala	gat gtt Asp Val 140	atg agt Met Ser	gcc ctg Ala Leu	432
cac gcc agc t His Ala Ser 1 145	tat gac gat Tyr Asp Asp 150	Gly Gln	tca ggc Ser Gly	gaa aaa Glu Lys 155	ttt ttg Phe Leu	cgg gaa Arg Glu 160	480
ctg tgc gaa q Leu Cys Glu V							528
gag acg aaa a Glu Thr Lys I	aac gag cag Asn Glu Glr 180	gtg gta Val Val	ctg cac Leu His 185	cag att Gln Ile	gtt gat Val Asp 190	cgc cgg Arg Arg	576
aca gcg tcg a Thr Ala Ser N 195							624
gcc atg aaa a Ala Met Lys 1 210							672
aac ggc ggg ( Asn Gly Gly 1 225	cga tgg gto Arg Trp Val 230	. Asn Phe	aac tgg Asn Trp	gag agc Glu Ser 235	tgg cgt Trp Arg	ccg aat Pro Asn 240	720
gtc gtc cag o			taa *				. 747
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tta atg gag Leu Met Glu							96

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		_		-		-	ctt Leu 40	-		-	_	_	_		-	144
	-			_	_		aag Lys	_			_	_		_		192
			_		-	-	aac Asn		_	_	_	_	_			240
_	_	-	_	_	_	-	atc Ile			-		-				288
							acg Thr									336
							ttt Phe 120									384
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							tgc Cys									480
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	gct gat Ala Asp 20	gcg aaa Ala Ly										96
gtt gcc gct Val Ala Ala 35												144
gtg cgt gaa Val Arg Glu 50	gcc acc Ala Thr	acc gcc Thr Ala	a Ser	ggc Gly	gtg ( Val /	gat Asp	aat Asn 60	gca Ala	gcc Ala	tcc Ser	ccc Pro	192
cga ctg gca Arg Leu Ala 65												240
ctg gta atg Leu Val Met		Ala Gl										288
gag cag tgt Glu Gln Cys			·					•				306
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ccg att gaa act aag cgt Pro Ile Glu Thr Lys Arg 100			
gat tat ctc gat gcg cca Asp Tyr Leu Asp Ala Pro 115			
ggg acg ttg tcg att atc Gly Thr Leu Ser Ile Met 130			
gtt aaa ccg ctg ttt gaa Val Lys Pro Leu Phe Glu 145	Leu Leu Gly Lys		
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ġcg ctc aat att gaa gcc Ala Leu Asn Ile Glu Ala 180		_	
gcc ggt gcg gac ccg gta Ala Gly Ala Asp Pro Val 195			
gct tcc tca cgt att ctc Ala Ser Ser Arg Ile Leu 210			<u>-</u>
acc ttt aat ccg ggc ttc Thr Phe Asn Pro Gly Phe 225 230	Lys Ile Ala Leu		
ctg gca ctg caa agt gcg Leu Ala Leu Gln Ser Ala 245		Leu Asn Leu Pro	
gcg acc tgc cag gag tta Ala Thr Cys Gln Glu Leu 260			
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-232-

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tta aaa caa cgt tat tcg ata cgt gaa att aag agg gat tta tgg Leu Lys Gln Arg Tyr Ser Ile Arg Glu Ile Lys Arg Asp Leu Trg 35 40 45	aac 144 Asn
atc aga gaa aac tat tcc agc aac gcg gct ata gcg aag atc tat Ile Arg Glu Asn Tyr Ser Ser Asn Ala Ala Ile Ala Lys Ile Tyr 50 55 60	tgc 192 Cys
cga aaa cgc aaa gcc agc gga cct gga aaa cat tta act att tta Arg Lys Arg Lys Ala Ser Gly Pro Gly Lys His Leu Thr Ile Leu 65 70 75	a cct 240 1 Pro 80
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					gtt Val											-·	816
					acc Thr												864
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			tct Ser													288
		_	atc Ile 100		_	_		_				-		_	-	336
			gaa Glu													384
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_	-	-	gtc Val				-	_			_	_			-	624
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		gat Asp 390						1200
		gga Gly						1248
		tat Tyr						1296
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		gtg Val						1392
		cgc Arg 470						1440
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		gag Glu						1536

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		aaa Lys														1632
		ctg Leu														1680
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	 -			ggc Gly 950	_	-	-	_		-			-	_	2880
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	 	_	-	ctg Leu	_	_	-			_			-	_	2976

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acc tcc agc ag Thr Ser Ser Se			•		-
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	ctg Leu															528
	gga Gly															576
	ctg Leu															624
	aat Asn 210															672
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	cag Gln	-	-										-	-	_	768
ggc Gly	gat Asp	gtg Val	gcg Ala 260	acg Thr	gtg Val	acc Thr	gac Asp	tca Ser 265	gtg Val	cag Gln	gat Asp	gtg Val	cgc Arg 270	aac Asn	gcc Ala	816
	atg Met															864
	gaa Glu 290															912
ccg Pro 305	gag Glu	ttg Leu	cag Gln	gaa Glu	acc Thr 310	att Ile	ccg Pro	gcg Ala	gcg Ala	att Ile 315	gat Asp	ctg Leu	caa Gln	att Ile	gcc Ala 320	960
	gat Asp															1008
	ctg Leu						Leu									1056
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	gac Asp															1248
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	acg Thr															1344
_	ctg Leu 450	_	_			_	_		-	_		_	_		-	1392
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	ggc Gly 530	-		-						_				_		1632
	tcg Ser															1680
	ggc Gly															1728
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					cag Gln											23	04
					aaa Lys											23	52
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gcc Ala	agt Ser	gcg Ala	gcg Ala 820	atc Ile	gat Asp	cgc Arg	gca Ala	atg Met 825	acc Thr	cag Gln	ctt Leu	ggt Gly	gtg Val 830	cct Pro	tcg Ser	24	96
					ttt Phe											25	44
atg	aac	tcg	cag	gtg	atc	ctg	att	atc	gcc	gcc	atc	gcc	acg	gtg	tat	25	92

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ctc tcc acc ctg ccc tcg gcg ggc gtt gga gcg ctg ttg gcg ctg gag Leu Ser Thr Leu Pro Ser Ala Gly Val Gly Ala Leu Leu Ala Leu Glu 885 890 895	2688
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_	_		-		tat Tyr		_					_	_		-	192
					gac Asp 70											240
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					gtc Val											384
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Ser Leu Ala Ser Thr Gln Ser Arg Arg His Leu Phe Gln Arg Ala Val
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65
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Val Leu Gly Val Thr Thr Ile Val Val Asp Ile Ile Val Met Ile Gly
tac gcc acc ctt gct caa cqq att gct cta tqq att aaa gga cca aag
                                                                      336
Tyr Ala Thr Leu Ala Gln Arg Ile Ala Leu Trp Ile Lys Gly Pro Lys
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                                                                      384
Gln Met Lys Ala Leu Asn Lys Ile Phe Gly Ser Leu Phe Met Leu Val
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	gcc Ala															144
	aaa Lys 50					_	-	_				-	-			192
	ctc Leu	_	_	_		-						_	-			240
	gcc Ala	-	_			_	-			-	-					288
-	aca Thr	_	-	_	_		_				_	-	-	-	-	336
	ccg Pro															384
	tgg Trp 130			_	_				_	_		_		_	_	432
	cat His															480
	gca Ala															528
_	ggg Gly		_		_	-		_		_			-			576
_	tac Tyr			_	-	-	-	_			_			-	-	624
	ttc Phe 210															672
	gaa Glu															720
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aag taa Lys *	774												
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gtt tct tcc ctg gct gtg ctg ttt agc ctg ccg ttt ggg atc ttt ttt Val Ser Ser Leu Ala Val Leu Phe Ser Leu Pro Phe Gly Ile Phe Phe 20 25 30	96												
gcc tgg tta ctg gtg cgt tgc acg ttt ccg ggc aaa gct ctg ctc gac Ala Trp Leu Leu Val Arg Cys Thr Phe Pro Gly Lys Ala Leu Leu Asp 35 40 45	144												
age gta etg cat eta eeg etg gtg tta eeg eee gtg gte gte ggt tae Ser Val Leu His Leu Pro Leu Val Leu Pro Pro Val Val Gly Tyr 50 55 60	192												
tta tta tta gtt tcg atg gga cgg cgc gga ttt atc ggt gaa cgt ctg Leu Leu Leu Val Ser Met Gly Arg Arg Gly Phe Ile Gly Glu Arg Leu 65 70 75 80	240												
tat gac tgg ttt ggt att acc ttc gcc ttt agc tgg cgc gcg gtt Tyr Asp Trp Phe Gly Ile Thr Phe Ala Phe Ser Trp Arg Gly Ala Val 85 90 95	288												
ctc gct gcc gcc gtc atg tcg ttt ccg ctg atg gtg cgg gca att cgt Leu Ala Ala Ala Val Met Ser Phe Pro Leu Met Val Arg Ala Ile Arg 100 105 110	336												
ctg gcg ctg gaa ggg gtt gat gtc aaa ctg gaa cag gcc gca aga aca Leu Ala Leu Glu Gly Val Asp Val Lys Leu Glu Gln Ala Ala Arg Thr 115 120 125	384												
ctg ggg gcc ggg cgc tgg cgc gtt ttc ttt act atc acg tta ccg ctg Leu Gly Ala Gly Arg Trp Arg Val Phe Phe Thr Ile Thr Leu Pro Leu 130 135 140	432												
acc tta ccg gga att att gtt ggt acg gta ctg gct ttt gct cgt tct Thr Leu Pro Gly Ile Ile Val Gly Thr Val Leu Ala Phe Ala Arg Ser 145 150 155	480												
ctc ggt gag ttt ggt gca acc atc acc ttt gtg tcg aac att cct ggt Leu Gly Glu Phe Gly Ala Thr Ile Thr Phe Val Ser Asn Ile Pro Gly 165 170 175	528												
gaa acg cga acc att cct tct gcc atg tat acc ctg atc cag acc ccc	576												

Glu Thr Arg Thr Ile 180	Pro Ser Ala	Met Tyr Thr I 185	Leu Ile Gln Thr 190	Pro									
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cgc ccg caa aaa ggg Arg Pro Gln Lys Gly 50													
gcc gaa aaa ggt atc Ala Glu Lys Gly Ile 65													
gtt ttt cag gat gcg Val Phe Gln Asp Ala 85													
ctg cgc tac ggc atg Leu Arg Tyr Gly Met 100													
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	130					135					14,0					
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	ccg Pro															528
gaa Glu	atc Ile	aac Asn	att Ile 180	ccg Pro	atg Met	ttg Leu	tat Tyr	gtc Val 185	agc Ser	cat His	tcg Ser	ctg Leu	gat Asp 190	gag Glu	atc Ile	576
	cat His															624
gcc Ala	ttt Phe 210	ggc Gly	gcg Ala	ctg Leu	gag Glu	gaa Glu 215	gtg Val	tgg Trp	ggc Gly	agt Ser	agc Ser 220	gtg Val	atg Met	aat Asn	ccg Pro	672
tgg Trp 225	ctg Leu	ccg Pro	aaa Lys	gag Glu	caa Gln 230	caa Gln	agt Ser	agc Ser	att Ile	ctg Leu 235	aaa Lys	gtg Val	acg Thr	gtg Val	ctt Leu 240	720
gag Glu	cat His	cat His	ccg Pro	cat His 245	tac Tyr	gcg Ala	atg Met	acc Thr	gcg Ala 250	ctg Leu	gcg Ala	ctg Leu	ggc Gly	gat Asp 255	cag Gln	768
cat His	ttg Leu	tgg Trp	gtc Val 260	aat Asn	aag Lys	ctg Leu	gac Asp	gaa Glu 265	ccg Pro	ctg Leu	caa Gln	gct Ala	gcg Ala 270	cta Leu	cgt Arg	816
atc Ile	cgc Arg	att Ile 275	cag Gln	gct Ala	tcc Ser	gat Asp	gtt Val 280	tct Ser	ctg Leu	gtt Val	tta Leu	caa Gln 285	ccg Pro	ccg Pro	cag Gln	864
	acc Thr 290															912
gac Asp 305	gac Asp	aac Asn	ggc Gly	cag Gln	gtg Val 310	gaa Glu	gtg Val	gaa Glu	ctg Leu	gaa Glu 315	gtc Val	ggc Gly	ggt Gly	aaa Lys	acg Thr 320	960
ctg Leu	tgg Trp	gcg Ala	cgt Arg	atc Ile 325	agc Ser	ccg Pro	tgg Trp	gcc Ala	agg Arg 330	gat Asp	gaa Glu	ctg Leu	gcg Ala	atc Ile 335	aaa Lys	1008
cct Pro	ggc Gly	ctg Leu	tgg Trp 340	ctg Leu	tac Tyr	gcg Ala	caa Gln	att Ile 345	aaa Lys	agt Ser	gtg Val	tcg Ser	ata Ile 350	acc Thr	gcc Ala	1056
tga *																1059

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gcg gat act aaa aca gga ggt ttt atg aac aga acg att ctt gtc cct
                                                                       96
Ala Asp Thr Lys Thr Gly Gly Phe Met Asn Arg Thr Ile Leu Val Pro
atc gat att tcc gat tca gaa tta act caa cgc gtg att agc cac gtt
                                                                      144
Ile Asp Ile Ser Asp Ser Glu Leu Thr Gln Arg Val Ile Ser His Val
         35
                              40
gag gaa gag gca aag att gat gat gca gag gtt cat ttc ctg acg gta
                                                                      192
Glu Glu Glu Ala Lys Ile Asp Asp Ala Glu Val His Phe Leu Thr Val
ata cct tca ctg ccc tac tat gcc tct ctg ggt tta gcg tat tcc gca
                                                                      240
Ile Pro Ser Leu Pro Tyr Tyr Ala Ser Leu Gly Leu Ala Tyr Ser Ala
gaa tta ccg gca atg gat gac ctg aaa gcg gaa gcc aaa tcg caa ctg
                                                                      288
Glu Leu Pro Ala Met Asp Asp Leu Lys Ala Glu Ala Lys Ser Gln Leu
                 85
                                     90
gaa gag atc att aaa aaa ttt aaa ctg cca acc gac aga gtg cat gtc
                                                                      336
Glu Glu Ile Ile Lys Lys Phe Lys Leu Pro Thr Asp Arg Val His Val
            100
                                105
cat gtt gag gaa ggc tcg ccc aaa gac cgc att ctg gaa ttg gcg aag
                                                                      384
His Val Glu Glu Gly Ser Pro Lys Asp Arg Ile Leu Glu Leu Ala Lys
aag atc ccc gct cat atg atc atc att gct tcc cat cga ccg gat atc
                                                                      432
Lys Ile Pro Ala His Met Ile Ile Ile Ala Ser His Arg Pro Asp Ile
                        135
acc act tat ctg ctc ggt tcc aac gcc gca gct gta gtg cgt cac gca
                                                                      480
Thr Thr Tyr Leu Leu Gly Ser Asn Ala Ala Ala Val Val Arg His Ala
                    150
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145
                                                                      507
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Glu Cys Ser Val Leu Val Val Arg *
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<212> DNA

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aat gac cag gtt aac cat Asn Asp Gln Val Asn His 225 230												
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atg tat tca gaa acg cgt Met Tyr Ser Glu Thr Arg 260												
gct gtg gca aac aaa acc Ala Val Ala Asn Lys Thr 275												
ttt gat ttt ggt ctg cgt Phe Asp Phe Gly Leu Arg 290												
cgt gac ctg cac gct gcg Arg Asp Leu His Ala Ala 305 310			-									
gat aaa gat ctg gtt aaa Asp Lys Asp Leu Val Lys 325												
aat aaa aac atg tcc acc Asn Lys Asn Met Ser Thr 340			-									
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Glu	Met	Ile 35	Leu	Val	Gln	Ser	Thr 40	Gly	Met	Ala	Gln	Trp 45	Leu	Gln	Met		
acc Thr	ctg Leu 50	tcg Ser	caa Gln	aag Lys	ttt Phe	ggt Gly 55	att Ile	gcg Ala	gca Ala	aac Asn	att Ile 60	gat Asp	ttt Phe	ccg Pro	ctg Leu	1	192
cca Pro 65	gcg Ala	agc Ser	ttt Phe	atc Ile	tgg Trp 70	gat Asp	atg Met	ttc Phe	gtc Val	cgg Arg 75	gtg Val	tta Leu	ccg Pro	gaa Glu	atc Ile 80	;	240
ccc Pro	aaa Lys	gag Glu	agc Ser	gcc Ala 85	ttt Phe	aac Asn	aaa Lys	cag Gln	agc Ser 90	atg Met	agc Ser	tgg Trp	aaa Lys	ctg Leu 95	atg Met	:	288
											ttt Phe					;	336
											ctg Leu					:	384
tca Ser	aaa Lys 130	gcg Ala	gcg Ala	gac Asp	ctg Leu	ttt Phe 135	gac Asp	cag Gln	tat Tyr	ctg Leu	gtc Val 140	tat Tyr	cgt Arg	ccg Pro	gac Asp	•	432
tgg Trp 145	ctg Leu	gca Ala	cag Gln	tgg Trp	gaa Glu 150	aca Thr	gga Gly	cat His	ttg Leu	gtt Val 155	gaa Glu	GJÀ aaa	ctg Leu	gga Gly	gaa Glu 160	ı	480
gca Ala	cag Gln	gcc Ala	tgg Trp	caa Gln 165	gcc Ala	ccg Pro	ttg Leu	tgg Trp	aag Lys 170	gcg Ala	ctg Leu	gtg Val	gaa Glu	tat Tyr 175	acc Thr	,	528
cat His	caa Gln	ctc Leu	ддд Glу 180	caa Gln	ccg Pro	cgc Arg	tgg Trp	cac His 185	cgc Arg	gcc Ala	aat Asn	ctc Leu	tat Tyr 190	cag Gln	cgc Arg		576
ttt Phe	atc Ile	gaa Glu 195	acg Thr	ctg Leu	gag Glu	tcc Ser	gcg Ala 200	acg Thr	acc Thr	tgc Cys	ccg Pro	ccg Pro 205	ggg Gly	tta Leu	cct Pro		624
tcg Ser	cgc Arg 210	gtc Val	ttt Phe	ata Ile	tgc Cys	ggt Gly 215	att Ile	tcc Ser	gcg Ala	tta Leu	ccg Pro 220	cct Pro	gtt Val	tat Tyr	ctc Leu		672
cag Gln 225	Ala	cta Leu	cag Gln	gcg Ala	ctg Leu 230	ggt Gly	aaa Lys	cat His	att Ile	gaa Glu 235	atc Ile	cat His	ctc Leu	ctg Leu	ttt Phe 240		720
acc Thr	aac Asn	ccc Pro	tgc Cys	cgt Arg 245	tat Tyr	tac Tyr	tgg Trp	ggc Gly	gat Asp 250	Ile	aaa Lys	gat Asp	cct Pro	gct Ala 255	Tyr		768
ctg Leu	gcg Ala	aaa Lys	ctg Leu 260	ctg Leu	acc Thr	cgt Arg	cag Gln	cgt Arg 265	Arg	cac His	agt Ser	ttt Phe	gaa Glu 270	Asp	cgc Arg		816
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Glu	Leu	Pro 275	Leu	Phe	Arg	Asp	Ser 280	Glu	Asn	Ala	Gly	Gln 285	Leu	Phe	Asn	
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				gac Asp												960
_		_	_	gcc Ala 325		-	-	_	_		-		_	_		1008
				gac Asp												1056
			_	gag Glu			-	_	-			_	_		_	1104
				agt Ser												1152
				tta Leu												1200
				ccg Pro 405												1248
				ttt Phe												1296
_				tac Tyr	-			_	_	_			_			1344
				gcg Ala												1392
				gat Asp		-		-	_	-		-		_		1440
				atc Ile 485												1488
				ggc Gly												1536
gag	ctg	gaa	ctc	ccc	gcc	acc	gga	caa	cac	acc	tgg	cga	ttt	ggc	ctg	1584

Glu	Leu	Glu 515	Leu	Pro	Ala	Thr	Gly 520	Gln	His	Thr	Trp	Arg 525	Phe	Gly	Leu	
						tac Tyr 535										1632
	_	-				gat Asp	-	_	_				-	-	-	1680
						ctg Leu										1728
						ccg Pro										1776
_	_			_		ttc Phe	-	_	-	-	-		-			1824
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						gcg Ala										1920
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						act Thr										2016
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						gac Asp 695										2112
						gac Asp										2160
						ctc Leu										2208
-	_		_	-	_	ttc Phe	_	_	-	_		_	-	_		2256
gac	tac	atc	ggg	caa	agt	cat	tat	cta	ccg	ggc	gat	gaa	gcg	ctc	aac	2304

Asp	Tyr	Ile 755	Gly	Gln	Ser	His	Tyr 760	Leu	Pro	Gly	Asp	Glu 765	Ala	Leu	Asn	
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														cga Arg		2400
														aaa Lys 815		2448
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	_						-	_			_	_		caa Gln		2640
	_	_		_		-	_	_		-	_	-	-	gaa Glu 895	-	2688
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	-				_		-	_	_		_	-	_	ctt Leu	-	2784
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_	_		-	_	-		_					-		gcc Ala 975	_	2928
	_				_	-			_		_	-	_	ggt Gly		2976
aat	ggt	gaa	agt	cgc	ctt	ttt	cta	cgc	aaa	gac	ggc	gag	tgg	cgt	ttt	3024

Asn Gly Glu Ser 995	Arg Leu	Phe Leu 100		Asp Gly	Glu Trp 1005	Arg Phe		
ccg ccg ctt gca Pro Pro Leu Ala 1010					Ser Gln		3072	
gag ggg tat cgt Glu Gly Tyr Arg 1025		Met Ser						
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atg ctg gat gac Met Leu Asp Asp 1060	Asp Ser				_	Phe Leu	3216	
cag gct tac gaa Gln Ala Tyr Glu 1075			Val Arg			_	3264	
tgg tat caa agg Trp Tyr Gln Arg 1090					Thr Met		3312	
atc gtt gaa cag Ile Val Glu Gln 1105	-	Arg Phe	-		_			
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= =	La coli						3369	
Gln Ser *  <210> 281 <211> 324 <212> DNA							3369	
<pre>Gln Ser *  &lt;210&gt; 281 &lt;211&gt; 324 &lt;212&gt; DNA &lt;213&gt; Escherichi &lt;220&gt; &lt;221&gt; CDS</pre>	l) ctg aag			e ttt agc v Phe Ser		gag gta		
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gcc cag gtt tg Ala Gln Val Cy 65			Asn Glu Ala	
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gga aac att gt Gly Asn Ile Va 10	l Phe Ser Pr		Ser Asp Phe	
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tgg cag cag tcg caa c Trp Gln Gln Ser Gln A 35			-
tat ttg ctc tat tta c Tyr Leu Leu Tyr Leu F 50	2 2 2		
agt atc agc gtt atc a Ser Ile Ser Val Ile A 65			
gct gct ggg gcc aat a Ala Ala Gly Ala Asn 1 85			
cca cgc tgg ccc gaa g Pro Arg Trp Pro Glu V 100			
ttc ttt ggc ctg cgc a Phe Phe Gly Leu Arg A 115			
aac tca acg ggc gag t Asn Ser Thr Gly Glu 1 130			
cgg ctt tgt cag caa c Arg Leu Cys Gln Gln C 145			471
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		gcc Ala													144
		gcc Ala													192
		ggc Gly													240
-	-	gaa Glu	-			_	_	_	-			-		-	288
_		atc Ile 100			_	_	_				_				336
		gaa Glu													384
_		acc Thr	_	_	_				_	_	•	_	-	-	432
		aac Asn			_	_	_			_	_	_		_	480
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	 _	gag Glu 180				-	-	_	- •	_	_				576
		gcg Ala													624
		tcc Ser													672
-	_	ccg Pro		_	-					_	-	_		-	720 ·
		ggg Gly													768

	245	250	255	
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aac gat cag gaa Asn Asp Gln Glu 275		n Ile Ser Leu (		
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caa acc gat atc Gln Thr Asp Ile 305				
cga tat ctt tcg Arg Tyr Leu Ser	ctg cat gat gaa Leu His Asp Glu 325			
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	aat att cga act Asn Ile Arg Thr 405			
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gaa tcg ctg ga Glu Ser Leu As 545	t aac ctg gtg p Asn Leu Val 550	gca acc to Ala Thr Se	c acc gcg ccg t r Thr Ala Pro E 555	tt atc acg 1680 he lle Thr 560
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tgg cct tcg gc Trp Pro Ser Al 595	a tca ctt tac a Ser Leu Tyr	gac tac cc Asp Tyr Pr 600	g ccg caa gaa c o Pro Gln Glu G 605	ag tgg aac 1824 In Trp Asn
gct ttc cag aa Ala Phe Gln Ly 610	a ctg gca caa s Leu Ala Gln 615	atg ctg at Met Leu Me	g cat acg ccg t t His Thr Pro E 620	tt aac gcc 1872 Phe Asn Ala
gag ggt atc gt Glu Gly Ile Va 625	c aca aaa atc l Thr Lys Ile 630	ttc act ga Phe Thr As	c gcc aat ggt a p Ala Asn Gly 1 635	cg cag cat 1920 Chr Gln His 640
att ggc ctt ca Ile Gly Leu Hi	t ccg atc ccg s Pro Ile Pro 645	gat cgt tc Asp Arg Se 65	c ggc ctg tgg c r Gly Leu Trp <i>F</i> O	egc tat ctc 1968 Arg Tyr Leu 655
agc acc aca tt Ser Thr Thr Le 66	u Leu Leu Leu	acg atg ct Thr Met Le 665	g ggt agc gcc a u Gly Ser Ala 1	itt tac aat 2016 Te Tyr Asn 570
ggc gta cag gc Gly Val Gln Al 675	c tgg cgt cgt a Trp Arg Arg	tac cag cg Tyr Gln Ar 680	t cat ege act of the state of t	ege atg atg 2064 Arg Met Met
gag att cag go Glu Ile Gln Al 690	c tat tat gaa a Tyr Tyr Glu 695	agc tgc ct Ser Cys Le	g aac ccg caa c u Asn Pro Gln I 700	etg atc acc 2112 Leu Ile Thr
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gca gcc ttg ctg Ala Ala Leu Leu					
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gac cga cgc ccg Asp Arg Arg Pro 115				eu Arg Phe 1	
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-269-

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Phe Ala Val Arg Gly Glu Leu Val Thr Val Ser Glu Thr Leu Gln Gln
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144

11e Leu Glu Asn His Asp Tyr Pro Gln Pro Val Lys Asn Val Leu Ala

35

40

45

gaa ctg ctg gtt gcg acc agc ctg tta acc gct acg ctg aag ttt gat
Glu Leu Leu Val Ala Thr Ser Leu Leu Thr Ala Thr Leu Lys Phe Asp
50 55 60

ggt gat atc acc gta cag ctg cag ggc gac ggt ccg atg aat ctg gcg 240 Gly Asp Ile Thr Val Gln Leu Gln Gly Asp Gly Pro Met Asn Leu Ala 65 70 75 80

gtt att aac ggt aac aat aac cag cag atg cgc ggt gtg gcg cgc gtg
Val Ile Asn Gly Asn Asn Gln Gln Met Arg Gly Val Ala Arg Val
85 90 95 .

cag ggc gaa att cca gaa aat gcc gac ctg aaa acg ctg gtc ggc aat 336 Gln Gly Glu Ile Pro Glu Asn Ala Asp Leu Lys Thr Leu Val Gly Asn 100 105

ggt tac gtg gtg atc acc att acc ccg agc gaa ggc gaa cgc tat cag
Gly Tyr Val Val Ile Thr Ile Thr Pro Ser Glu Gly Glu Arg Tyr Gln
115 120 125

ggc gta gtt ggt ctg gaa ggt gat acc ctg gcg gcc tgc ctg gaa gat 432 Gly Val Val Gly Leu Glu Gly Asp Thr Leu Ala Ala Cys Leu Glu Asp 130 135 140

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Tyr Phe Met Arg Ser Glu Gln Leu Pro Thr Arg Leu Phe Ile Arg Thr
145 150 155 160

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atg cct gcg caa aat gcc cag cag gac gac ttt gac cac ctg gcg acg

Met Pro Ala Gln Asn Ala Gln Gln Asp Asp Phe Asp His Leu Ala Thr

180

185

190

cta acc gaa acc atc aaa acc gaa gaa ctg ctg acc tta ccg gca aac 624 Leu Thr Glu Thr Ile Lys Thr Glu Glu Leu Leu Thr Leu Pro Ala Asn

gaa gtg ttg tgg cgt ttg tat cac gaa gaa gag gtg acg gtt tac gat 672

210	Arg Leu	Tyr His 215	Glu G	Glu Glu	Val Th 220	nr Val	Tyr	Asp	
ccg cag gat gte Pro Gln Asp Vai 225	gag ttc Glu Phe 230	aaa tgc Lys Cys	acc t	tgc tcg Cys Ser 235	cgt ga Arg Gl	aa cgt lu Arg	tgc Cys	gcc Ala 240	720
gat gcg ctg aaa Asp Ala Leu Ly:			Glu G						768
gaa gat ggc gaa Glu Asp Gly Glu 260	Ile Asp								816
ctg ttc aat gcg Leu Phe Asn Ala 275			Glu I		Asn As				864
gca gat ccg ca Ala Asp Pro Gli 290		taa *	·						885
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	att Ile															96
_	gtg Val	-		-				-		-		-	-	_		144
	atc Ile 50			-	_	_	-		-			_	-	_	_	192
	ttt Phe		_					-		_	_		-			240
	cat His															288
	ccg Pro															336
_	gat Asp	_	-		_		-		-	_			_		_	384
	aag Lys 130															432
	aat Asn															480
_	gat Asp	-	-	-					-		_	_				528

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cct ctt cgc a Pro Leu Arg I 225					-	Val A	
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gct gtt agg g Ala Val Arg G		Ser Leu					
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gga aga gcc a Gly Arg Ala I 35							

						aaa Lys 55										192
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						act Thr										288
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	-			-		tct Ser 135				_		_		-		432
						gtt Val							_			480
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						att Ile			-	_						624
		-		-		gtg Val 215	-	_						_		672
					-	gtt Val	-			_			-			720
		-				atg Met							_		-	768
	-	-	-	_	_	gtt Val			-	-						816
_					-	acc Thr			_	_		_	_	_		864

					gaa Glu											912
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					aat Asn											1008
					aac Asn											1056
					att Ile	-				_						1104
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					cca Pro											96
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	Lys Thr Va			ggt gaa cgc Gly Glu Arg	
gcg acg ctg Ala Thr Leu	ggg cgt ct Gly Arg Le 85	t atg agc u Met Ser	ctg ctg tca Leu Leu Ser 90	ccc ttt gac Pro Phe Asp	gtg gtg 288 Val Val 95
				tcc cgc ctg Ser Arg Leu 110	
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	aat Asn 50															192
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	cgg Arg															288
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	agt Ser															384
	gag Glu 130															432
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gcg Ala	ctg Leu	ccg Pro	gaa Glu	gaa Glu 165	ctc Leu	cgc Arg	tta Leu	agt Ser	ccg Pro 170	cat His	cgt Arg	tat Tyr	ctg Leu	gcg Ala 175	aca Thr	528
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gaa Glu 225	gcc Ala	gcc Ala	ggt Gly	gaa Glu	ttc Phe 230	agc Ser	ggc Gly	gaa Glu	atc Ile	acc Thr 235	ggc Gly	gtg Val	acg Thr	gat Asp	ggt Gly 240	720
	tgg Trp															768
gaa	gaa	gcc	cgg	cag	cag	gcc	att.	tcc	ggc	<b>ggg</b>	acg	gaa	ccg	tcc	gct	816

Glu	Glu	Ala	Arg 260	Gln	Gln	Ala	Ile	Ser 265	Gly	Gly	Thr	Glu	Pro 270	Ser	Ala	
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						tgg Trp 295										912
			-		_	ctg Leu		_				-		_		960
						gac Asp										1008
						cgg Arg										1056
						tac Tyr										1104
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_	_					gac Asp	-	_	_	_	_	_		-		1200
_	_		-	-		ctg Leu	-					_	-			1248
_		_	-	•	-	agt Ser	-		-	-						1296
						ggc Gly										1344
						cgc Arg 455										1392
						cac His										1440
_		-	-	-	_	cgg Arg	_		-	-	-		_	_		1488
cag	gaa	act	gcc	cct	gac	ggc	gat	atc	acc	cgc	tac	cgt	tat	gat	aat	1536

Gln	Glu	Thr	Ala 500	Pro	Asp	Gly	Asp	Ile 505	Thr	Arg	Tyr	Arg	Tyr 510	Asp	Asn	
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		-	_		agc Ser	_			_	_	-	_			•	1632
					acc Thr 550											1680
					gag Glu											1728
_	_		-		att Ile	_			_	_	-			_	_	1776
					atc Ile											1824
-		-	_		Gly ggg		_		_				_	-	_	1872
cgt Arg 625	acc Thr	acg Thr	cag Gln	ggc Gly	ggg Gly 630	cta Leu	acg Thr	cgc Arg	agt Ser	atg Met 635	gaa Glu	tac Tyr	gat Asp	gct Ala	gcc Ala 640	1920
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					cac His											2064
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					ctg Leu											2208
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cat His	gag Glu 770	acc Thr	aga Arg	cat His	gcg Ala	tac Tyr 775	aac Asn	gcg Ala	cag Gln	ggg Gly	ctg Leu 780	gcg Ala	aac Asn	cgc Arg	tgt Cys	2352
ata Ile 785	ccg Pro	gac Asp	agc Ser	ctg Leu	ccc Pro 790	gcc Ala	gtg Val	gaa Glu	tgg Trp	ctg Leu 795	acc Thr	tac Tyr	ggc Gly	agc Ser	ggt Gly 800	2400
tac Tyr	ctg Leu	gca Ala	ggc Gly	atg Met 805	aaa Lys	ctc Leu	ggc Gly	gac Asp	aca Thr 810	ccg Pro	ctg Leu	gtg Val	gag Glu	tac Tyr 815	acc Thr	2448
	gac Asp															2496
	acc Thr															2544
	agc Ser 850															2592
	atc Ile															2640
	acc Thr															2688
	cgc Arg															2736
	gag Glu															2784
	gcc Ala 930	_	-								_	-				2832
	aca Thr															2880
	gag Glu															2928
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His Tyr Thi	Arg Thr 980	Gln Tyr	Glu Glu 985		Val Glu	Ser Ar 990	g Tyr	
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gaa cgg gad Glu Arg Asg 1010			Met Ser	_		-		3072
acc tgg tac Thr Trp Tyr 1025				-	Thr Ile	_	-	3120
aga acc cgc Arg Thr Arc	atc cag Ile Gln 104	Thr Ile	tat cag Tyr Gln	ccg ggg Pro Gly 1050	agc ttc Ser Phe	acg cc Thr Pr	o Leu	3168
atc aga gtt Ile Arg Val				Leu Ala				3216
agc ctg gcg Ser Leu Ala 107	Asp Ala	-	-			Gly Gl	-	3264
gtg gtg tto Val Val Phe 1090			Val Gln	_			-	3312
gaa atc ctg Glu Ile Leu 1105				-	Arg Arg			3360
tcg tgc ggc Ser Cys Gly		Val Glu					o Val	3408
tac acg ccg Tyr Thr Pro			_	Tyr His		_		3456
ctg ccg ctg Leu Pro Leu 115	Ala Leu	atc agc Ile Ser	aag gaa Lys Glu 1160	ggg aca Gly Thr	aca gaa Thr Glu 116	Trp Cy	c gca s Ala	3504
gaa tac gat Glu Tyr Asp 1170			Leu Leu					3552
ctg cag cag Leu Gln Glr 1185					Tyr Asp			3600
ggc ctg tat Gly Leu Tyr		Arg His	_	_			y Arg	3648
tat atc act	cag gat	ccg att	ggg ctg	aag ggg	gga tgg	aat tt	t tat	3696 .

Tyr Ile Thr Gln Asp Pro Ile Gly Leu Lys Gly Gly Trp Asn Phe Tyr

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	ttt Phe 1250	Pro					Leu					Pro				3792
	cag Gln					Asp					Āla					3840
	aac Asn				Ser					Asp					Asn	3888
	ccg Pro			Āla					Met					Gly		3936
	gca Ala		Thr					Arg					Ile			3984
	ttc Phe 1330	Trp					Lys					Asp				4032
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aga Arg	tag *															4134
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	aat Asn															96

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					caa Gln												432
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					atc Ile												672
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atc Ile	att Ile	gaa Glu	gct Ala	gcg Ala 245	ggt Gly	gaa Glu	tta Leu	ggt Gly	gat Asp 250	aaa Lys	acg Thr	cta Leu	ctt Leu	cct Pro 255	gtt Val		768
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				tgc Cys												192
_	_			aca Thr			_	-	-		_	_				240
				gag Glu 85												288
		Gln	Gln	tat Tyr	Asp	Glu	Glu	Ser	Gly	Leu	Tyr		Asn	Arg		336
				ccg Pro												384
				gga Gly												432
		_	_	ccg Pro			_	-	_						_	480
-	-			cat His 165		-	_	_							-	528

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Val Glu A 50	sn Asp	Gly	Gly	Ser 55	Leu	Glu	Ala	Ile	Ala 60	Lys	Lys	Tyr	Asn	
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Pro Asp A	100	-				105					110			
_	15				120					125				
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Thr Val S 145			150					155					160	
Ile Arg A		165					170					175		
Pro Ala G	180					185					190			
	95				200					205				
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Ile Lys T 225	nr Leu	Pne	230	GIN	val	Inr	PLO	235	Int	ьуз	Vai	ASII	240	
Ile Asn T	hr Pro	Ile 245		Val	Ser	Ala	Glu 250		Asn	Gly	Ala	Arg 255		
Val Glu V	al His 260	Gln	Pro	Leu	Ser	Glu 265		Ile	Asp	Asp	Asp 270		Gln	
Leu Leu P 2	ro Ile 75	Thr	Leu	Asn	Ser 280	Ala	Met	Gln	Ser	Phe 285	Ľуз	Asp	Ala	

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390

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Ile Phe Asn Ser Leu Ser Glu Thr Gly Tyr Glu Gly Leu Leu Ser Lys
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Lys Asn Leu Met His Ile Leu Glu Ala Lys Asp Lys Asn Gly Phe Ser
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                               445
Ile Leu Asn Ala Leu Pro Lys Leu Ala Ala Thr His His Leu Asp Asn
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                                   460
Glu Gln Val Tyr Lys Phe Leu Ser Ala Lys Asn Arg Thr Ser Ser His
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                                  475
Val Leu Tyr His Val Met Ala Asn Gly Asp Ala Asp Met Leu Lys Ile
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Val Leu Asn Ala Leu Pro Leu Leu Ile Arg Thr Cys His Leu Thr Lys
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Glu Gln Val Leu Asp Leu Leu Lys Ala Lys Asp Phe Tyr Gly Cys Pro
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Gly Leu Tyr Leu Ala Met Gln Asn Gly His Ser Asp Ile Val Lys Val
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Ile Leu Glu Ala Leu Pro Ser Leu Ala Gln Glu Ile Asn Ile Ser Ala
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Ser Asp Ile Val Asp Leu Leu Thr Ala Lys Ser Leu Ala Arg Asp Thr
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Gly Leu Phe Met Ala Met Gln Arg Gly His Met Asn Val Ile Asn Thr
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Ile Phe Asn Ala Leu Pro Thr Leu Phe Asn Thr Phe Lys Phe Asp Lys
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Lys Asn Met Lys Pro Leu Leu Leu Ala Asn Asn Ser Asn Glu Tyr Pro
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Gly Leu Phe Ser Ala Ile Gln His Lys Gln Gln Asn Val Val Glu Thr
625 630
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Val Tyr Leu Ala Leu Ser Asp His Ala Arg Leu Phe Gly Phe Thr Ala
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Glu Asp Ile Met Asp Phe Trp Gln His Lys Ala Pro Gln Lys Tyr Ser
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Ala Phe Glu Leu Ala Phe Glu Phe Gly His Arg Val Ile Ala Glu Leu
     675 680
Ile Leu Asn Thr Leu Asn Lys Met Ala Glu Ser Phe Gly Phe Thr Asp
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Glu Asn Asn Glu Cys Gly Ile Gly Asp Val Val Glu Ile Arg Glu Cys
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Gly Glu Asp Val Glu Lys Leu Arg Lys Val Val Ala Asp Ile Ala Gly

75

70

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Val Pro Ala Gln Ile Asn Ile Ala Glu Val Arg Lys Pro Glu Leu Asp
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Ala Lys Leu Val Ala Asp Ser Ile Thr Ser Gln Leu Glu Arg Arg Val
                         120
Met Phe Arg Arg Ala Met Lys Arg Ala Val Gln Asn Ala Met Arg Leu
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                                      140
Gly Ala Lys Gly Ile Lys Val Glu Val Ser Gly Arg Leu Gly Gly Ala
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Glu Ile Ala Arg Thr Glu Trp Tyr Arg Glu Gly Arg Val Pro Leu His
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Thr Leu Arg Ala Asp Ile Asp Tyr Asn Thr Ser Glu Ala His Thr Thr
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Tyr Gly Val Ile Gly Val Lys Val Trp Ile Phe Lys Gly Glu Ile Leu
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Asp Ile Asp Asp Leu Lys Val Thr Lys Ile Phe Val Asp Glu Gly Pro
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Ile Ala Val His Asn Gly Arg Gln His Val Pro Val Phe Val Thr Asp
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Arg Gly His Ala Ala Asp Lys Lys Ala Lys Lys
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Ile Thr Thr Arg His Ile Gly Gly Gly His Lys Gln Ala Tyr Arg Ile
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Val Asp Phe Lys Arg Asn Lys Asp Gly Ile Pro Ala Val Val Glu Arg
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Leu Glu Tyr Asp Pro Asn Arg Ser Ala Asn Ile Ala Leu Val Leu Tyr
Lys Asp Gly Glu Arg Arg Tyr Ile Leu Ala Pro Lys Gly Leu Lys Ala
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Gly Asp Gln Ile Gln Ser Gly Val Asp Ala Ala Ile Lys Pro Gly Asn
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                                              125
Thr Leu Pro Met Arg Asn Ile Pro Val Gly Ser Thr Val His Asn Val
                      135
                                          140
Glu Met Lys Pro Gly Lys Gly Gly Gln Leu Ala Arg Ser Ala Gly Thr
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                                      155
Tyr Val Gln Ile Val Ala Arg Asp Gly Ala Tyr Val Thr Leu Arg Leu
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               165
Arg Ser Gly Glu Met Arg Lys Val Glu Ala Asp Cys Arg Ala Thr Leu
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                               185
Gly Glu Val Gly Asn Ala Glu His Met Leu Arg Val Leu Gly Lys Ala
                           200
Gly Ala Ala Arg Trp Arg Gly Val Arg Pro Thr Val Arg Gly Thr Ala
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                                           220
Met Asn Pro Val Asp His Pro His Gly Gly Glu Gly Arg Asn Phe
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                                      235
Gly Lys His Pro Val Thr Pro Trp Gly Val Gln Thr Lys Gly Lys Lys
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                           40
Lys Leu Phe Glu Val Glu Val Glu Val Asn Thr Leu Val Val Lys
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Ser Lys Gly Lys Gly Phe Ala Gly Thr Val Lys Arg Trp Asn Phe Arg

Thr Gln Asp Ala Thr His Gly Asn Ser Leu Ser His Arg Val Pro Gly

120

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                                  170
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Gly Ala Gln Val Arg Gly Pro Ile Pro Leu Pro Thr Arg Lys Glu Arg
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Phe Thr Val Leu Ile Ser Pro His Val Asn Lys Asp Ala Arg Asp Gln
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Tyr Glu Ile Arg Thr His Leu Arg Leu Val Asp Ile Val Glu Pro Thr
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Asp Val Gln Ile Ser Leu Gly
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Tyr Ser Val Phe Thr Phe Gln Arg Met Lys Phe Met Asn Arg Thr Ser
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Pro Tyr Tyr Cys Arg Arg Ser Val Leu Ser Leu Leu Ile Ser Ala Leu
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Ile Tyr Ala Pro Pro Gly Met Ala Ala Phe Thr Thr Asn Val Ile Gly
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                                      75
Val Val Asn Asp Glu Thr Val Asp Gly Asn Gln Lys Val Asp Glu Arg
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Gly Thr Thr Asn Asn Thr His Ile Ile Asn His Gly Gln Gln Asn Val
                              105
His Gly Gly Val Ser Asn Gly Ser Leu Ile Glu Ser Gly Gly Tyr Gln
                        120
Asp Ile Gly Ser His Asn Asn Phe Val Gly Gln Ala Asn Asn Thr Thr
            135
                                         140
Ile Asn Gly Gly Arg Gln Ser Ile His Asp Gly Gly Ile Ser Thr Gly
              150 155
Thr Thr Ile Glu Ser Gly Asn Gln Asp Val Tyr Lys Gly Gly Ile Ser
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				165					170					175	
Asn	Gly	Thr	Thr 180	Ile	Lys	Gly	Gly	Ala 185	Ser	Arg	Val	Glu	Gly 190	Gly	Ser
Ala	Asn	Gly 195	Ile	Leu	Ile	Asp	Gly 200	Gly	Ser	Gln	Ile	Val 205	Lys	Val	Gln
Gly	His 210	Ala	Asp	Gly	Thr	Thr 215	Ile	Asn	Lys	Ser	Gly 220	Ser	Gln	Asp	Val
225		_		Leu	230					235		_	_		240
				Ser 245					250			_		255	_
			260	Tyr				265					270		_
		275		Leu			280					285			
_	290	_		Thr		295					300			_	
305			_	Ser	310					315	٠.	-			320
				Gln 325					330					335	
_			340	Ser Asp	_			345		_			350		
		355		Gly			360					365			_
	370			Leu		375					380	_	_	_	_
385					390			-		395			_		400
	_	_		Met 405					410					415	
			420	Gln				425					430		
		435		Gly			440					445			
	450			Ser		455					460				
465			_	Ser	470					475					480
	_	_		Ala 485		-			490					495	
			500	Gly				505					510		
		515		Ile			520					525			
	530	_		Leu		535					540		_		
545				Gly	550					555					560
_				Leu 565					570					575	
_			580	His				585					590		
		595		Gly			600					605			
	610			Arg		615					620				
625				Thr	630					635					640
Ile	Asn	Ala	Asn	Gly	гàг	Met	Asp	val	Tyr	GTĀ	ьуs	Asp	val	GTA	Thr

645 650 Val Leu Asn Ser Ala Gly Thr Gln Thr Ile Tyr Ala Ser Ala Thr Ser 665 Asp Lys Ala Asn Ile Lys Gly Gly Lys Gln Thr Val Tyr Gly Leu, Ala 680 Thr Glu Ala Asn Ile Glu Ser Gly Glu Gln Ile Val Asp Gly Gly Ser 695 700 Thr Glu Lys Thr His Ile Asn Gly Gly Thr Gln Thr Val Gln Asn Tyr 715 710 Gly Lys Ala Ile Asn Thr Asp Ile Val Ser Gly Leu Gln Gln Ile Met 730 Ala Asn Gly Thr Ala Glu Gly Ser Ile Ile Asn Gly Gly Ser Gln Val 745 Val Asn Glu Gly Gly Leu Ala Glu Asn Ser Val Leu Asn Asp Gly Gly 760 765 Thr Leu Asp Val Arg Glu Lys Gly Ser Ala Thr Gly Ile Gln Gln Ser 775 780 Ser Gln Gly Ala Leu Val Ala Thr Thr Arg Ala Thr Arg Val Thr Gly 790 795 Thr Arg Ala Asp Gly Val Ala Phe Ser Ile Glu Gln Gly Ala Ala Asn 805 810 Asn Ile Leu Leu Ala Asn Gly Gly Val Leu Thr Val Glu Ser Asp Thr 825 820 Ser Ser Asp Lys Thr Gln Val Asn Met Gly Gly Arg Glu Ile Val Lys 840 Thr Lys Ala Thr Ala Thr Gly Thr Thr Leu Thr Gly Gly Glu Gln Ile 855 860 Val Glu Gly Val Ala Asn Glu Thr Thr Ile Asn Asp Gly Gly Ile Gln 870 875 Thr Val Ser Ala Asn Gly Glu Ala Ile Lys Thr Lys Ile Asn Glu Gly 885 890 Gly Thr Leu Thr Val Asn Asp Asn Gly Lys Ala Thr Asp Ile Val Gln 900 905 Asn Ser Gly Ala Ala Leu Gln Thr Ser Thr Ala Asn Gly Ile Glu Ile 920 925 915 Ser Gly Thr His Gln Tyr Gly Thr Phe Ser Ile Ser Gly Asn Leu Ala 935 940 Thr Asn Met Leu Leu Glu Asn Gly Gly Asn Leu Leu Val Leu Ala Gly 950 Thr Glu Ala Arg Asp Ser Thr Val Gly Lys Gly Gly Ala Met Gln Asn 965 970 Leu Gly Gln Asp Ser Ala Thr Lys Val Asn Ser Gly Gly Gln Tyr Thr 980 985 Leu Gly Arg Ser Lys Asp Glu Phe Gln Ala Leu Ala Arg Ala Glu Asp 1000 1005 Leu Gln Val Ala Gly Gly Thr Ala Ile Val Tyr Ala Gly Thr Leu Ala 1015 Asp Ala Ser Val Ser Gly Ala Thr Gly Ser Leu Ser Leu Met Thr Pro 1035 1030 Arg Asp Asn Val Thr Pro Val Lys Leu Glu Gly Ala Val Arg Ile Thr 1050 1045 Asp Ser Ala Thr Leu Thr Leu Gly Asn Gly Val Asp Thr Thr Leu Ala 1065 1070 Asp Leu Thr Ala Ala Ser Arg Gly Ser Val Trp Leu Asn Ser Asn Asn 1080 1085 Ser Cys Ala Gly Thr Ser Asn Cys Glu Tyr Arg Val Asn Ser Leu Leu 1095 1100 Leu Asn Asp Gly Asp Val Tyr Leu Ser Ala Gln Thr Ala Ala Pro Ala 1110 1115 1120 Thr Thr Asn Gly Ile Tyr Asn Thr Leu Thr Thr Asn Glu Leu Ser Gly

	1125	113	0	1135
Ser Gly Asn Phe	Tyr Leu His			Arg Gly Asp 1150
Gln Leu Val Val 1155		Ala Thr Gly 1160	Asn Phe Lys	
Gln Asp Thr Gly 1170	Val Ser Pro 1175		Asp Ala Met 1180	Thr Leu Val
Lys Thr Gly Gly 1185	1190		1195	1200
Phe Val Asp Leu	Gly Thr Tyr 1205	Glu Tyr Val 121		Asp Gly Asn 1215
Ser Asn Trp Asn 122	0	1225		1230
Pro Asn Pro Lys 1235		1240	1245	5
Pro Lys Pro Asp 1250	1255	5	1260	
Lys Arg Ile Thr 1265	1270		1275	1280
Leu Pro Leu Val	1285	129	0	1295
Asn Ile Met Lys 130	0	1305		1310
Tyr Asn Thr Arg 1315		1320	1325	5
Gln Thr Leu Thr 1330	1335	5	1340	
Pro Glu Gly Ile 1345	1350		1355	1360
His Ile Gly Phe	1365	137	0	1375
Leu Gly Gly Tyr 138	0	1385		1390
Gly Val Val Lys		1400	140	5
Ser Ser Gly Gly	1415	5	1420	
Gly His Ile Glu 1425	1430		1435	1440
Thr Pro Tyr Ala	1445	145	0	1455
His Leu Ser Asn 146	0	1465		1470
Tyr Arg Glu Leu 1475		1480	148	5
Gly Met Glu Val 1490	1495	5	1500	
Val Asp Asp Asn 1505	1510		1515	1520
Tyr Leu Ser Gly	1525 ·	153	10	1535
Phe Ser Ser Thr 154	0	1545		1550
Ala Gly Val Glu 1555	Ser Pro Trp	Asn Ala Val 1560	. Ala Gly Val 156	Asn Trp Ser 5
Phe				

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345
Val Pro Gly Ile Arg Pro Gly Glu Gln Thr Ala Lys Tyr Ile Asp Lys
                                  365
                360
Val Met Thr Arg Leu Thr Leu Val Gly Ala Leu Tyr Ile Thr Phe Ile
                               380
            375
Cys Leu Ile Pro Glu Phe Met Arg Asp Ala Met Lys Val Pro Phe Tyr
        390
                                    395
Phe Gly Gly Thr Ser Leu Leu Ile Val Val Val Ile Met Asp Phe
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Met Ala Gln Val Gln Thr Leu Met Met Ser Ser Gln Tyr Glu Ser Ala
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Leu Lys Lys Ala Asn Leu Lys Gly Tyr Gly Arg
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                        440
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Lys Arg Leu Gly Arg Gly Ile Gly Ser Gly Leu Gly Lys Thr Gly Gly
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Arg Gly His Lys Gly Gln Lys Ser Arg Ser Gly Gly Gly Val Arg Arg
                         40
Gly Phe Glu Gly Gly Gln Met Pro Leu Tyr Arg Arg Leu Pro Lys Phe
                     55
Gly Phe Thr Ser Arg Lys Ala Ala Ile Thr Ala Glu Ile Arg Leu Ser
Asp Leu Ala Lys Val Glu Gly Gly Val Val Asp Leu Asn Thr Leu Lys
              85
                                90
Ala Ala Asn Ile Ile Gly Ile Gln Ile Glu Phe Ala Lys Val Ile Leu
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Ala Gly Glu Val Thr Thr Pro Val Thr Val Arg Gly Leu Arg Val Thr
 115 120
                                            125
Lys Gly Ala Arg Ala Ala Ile Glu Ala Ala Gly Gly Lys Ile Glu Glu
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Leu Pro Lys His Lys Ala Thr Leu Leu Gly Leu Gly Leu Arg Arg Ile
                             25
Gly His Thr Val Glu Arg Glu Asp Thr Pro Ala Ile Arg Gly Met Ile
                         40
Asn Ala Val Ser Phe Met Val Lys Val Glu Glu
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<210> 317
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Met Ala His Ile Glu Lys Gln Ala Gly Glu Leu Gln Glu Lys Leu Ile
Ala Val Asn Arg Val Ser Lys Thr Val Lys Gly Gly Arg Ile Phe Ser
Phe Thr Ala Leu Thr Val Val Gly Asp Gly Asn Gly Arg Val Gly Phe
Gly Tyr Gly Lys Ala Arg Glu Val Pro Ala Ala Ile Gln Lys Ala Met
Glu Lys Ala Arg Arg Asn Met Ile Asn Val Ala Leu Asn Asn Gly Thr
Leu Gln His Pro Val Lys Gly Val His Thr Gly Ser Arg Val Phe Met
                                   90
Gln Pro Ala Ser Glu Gly Thr Gly Ile Ile Ala Gly Gly Ala Met Arg
                               105
Ala Val Leu Glu Val Ala Gly Val His Asn Val Leu Ala Lys Ala Tyr
                            120
       115
Gly Ser Thr Asn Pro Ile Asn Val Val Arg Ala Thr Ile Asp Gly Leu
Glu Asn Met Asn Ser Pro Glu Met Val Ala Ala Lys Arg Gly Lys Ser
                   150
                                       155
Val Glu Glu Ile Leu Gly Lys
               165
<210> 318
<211> 117
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Met Asp Lys Lys Ser Ala Arg Ile Arg Arg Ala Thr Arg Ala Arg Arg
Lys Leu Gln Glu Leu Gly Ala Thr Arg Leu Val Val His Arg Thr Pro
Arg His Ile Tyr Ala Gln Val Ile Ala Pro Asn Gly Ser Glu Val Leu
                           40
Val Ala Ala Ser Thr Val Glu Lys Ala Ile Ala Glu Gln Leu Lys Tyr
Thr Gly Asn Lys Asp Ala Ala Ala Ala Val Gly Lys Ala Val Ala Glu
Arg Ala Leu Glu Lys Gly Ile Lys Asp Val Ser Phe Asp Arg Ser Gly
                                   90
Phe Gln Tyr His Gly Arg Val Gln Ala Leu Ala Asp Ala Ala Arg Glu
                              105
Ala Gly Leu Gln Phe
       115
<210> 319
<211> 177
<212> PRT
<213> Escherichia coli
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Met Ser Arg Val Ala Lys Ala Pro Val Val Pro Ala Gly Val Asp
                                    10
Val Lys Ile Asn Gly Gln Val Ile Thr Ile Lys Gly Lys Asn Gly Glu
                                25
Leu Thr Arg Thr Leu Asn Asp Ala Val Glu Val Lys His Ala Asp Asn
                           40
Thr Leu Thr Phe Gly Pro Arg Asp Gly Tyr Ala Asp Gly Trp Ala Gln
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Ala Gly Thr Ala Arg Ala Leu Leu Asn Ser Met Val Ile Gly Val Thr
Glu Gly Phe Thr Lys Lys Leu Gln Leu Val Gly Val Gly Tyr Arg Ala
Ala Val Lys Gly Asn Val Ile Asn Leu Ser Leu Gly Phe Ser His Pro
          100
                       105
Val Asp His Gln Leu Pro Ala Gly Ile Thr Ala Glu Cys Pro Thr Gln
                        120
                                          125
Thr Glu Ile Val Leu Lys Gly Ala Asp Lys Gln Val Ile Gly Gln Val
                       135
Ala Ala Asp Leu Arg Ala Tyr Arg Arg Pro Glu Pro Tyr Lys Gly Lys
                   150
                                      155
Gly Val Arg Tyr Ala Asp Glu Val Val Arg Thr Lys Glu Ala Lys Lys
                                  170
<210> 320
<211> 130
<212> PRT
<213> Escherichia coli
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Met Ser Met Gln Asp Pro Ile Ala Asp Met Leu Thr Arg Ile Arg Asn
                                  10
Gly Gln Ala Ala Asn Lys Ala Ala Val Thr Met Pro Ser Ser Lys Leu
Lys Val Ala Ile Ala Asn Val Leu Lys Glu Glu Gly Phe Ile Glu Asp
                           40
Phe Lys Val Glu Gly Asp Thr Lys Pro Glu Leu Glu Leu Thr Leu Lys
                      55
Tyr Phe Gln Gly Lys Ala Val Val Glu Ser Ile Gln Arg Val Ser Arg
                  70
Pro Gly Leu Arg Ile Tyr Lys Arg Lys Asp Glu Leu Pro Lys Val Met
              85
                                 90
Ala Gly Leu Gly Ile Ala Val Val Ser Thr Ser Lys Gly Val Met Thr
        100
                           105 110
Asp Arg Ala Ala Arg Gln Ala Gly Leu Gly Gly Glu Ile Ile Cys Tyr
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Val Ala
   130
<210> 321
<211> 101
<212> PRT
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Met Ala Lys Gln Ser Met Lys Ala Arg Glu Val Lys Arg Val Ala Leu
                                  10
Ala Asp Lys Tyr Phe Ala Lys Arg Ala Glu Leu Lys Ala Ile Ile Ser
          20
                               25
Asp Val Asn Ala Ser Asp Glu Asp Arg Trp Asn Ala Val Leu Lys Leu
                          40
Gln Thr Leu Pro Arg Asp Ser Ser Pro Ser Arg Gln Arg Asn Arg Cys
                       55
                                          60
Arg Gln Thr Gly Arg Pro His Gly Phe Leu Arg Lys Phe Gly Leu Ser
Arg Ile Lys Val Arg Glu Ala Ala Met Arg Gly Glu Ile Pro Gly Leu
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Lys Lys Ala Ser Trp 100 <210> 322 <211> 179 <212> PRT <213> Escherichia coli <400> 322 Met Ala Lys Leu His Asp Tyr Tyr Lys Asp Glu Val Val Lys Lys Leu Met Thr Glu Phe Asn Tyr Asn Ser Val Met Gln Val Pro Arg Val Glu 25 Lys Ile Thr Leu Asn Met Gly Val Gly Glu Ala Ile Ala Asp Lys Lys 40 Leu Leu Asp Asn Ala Ala Ala Asp Leu Ala Ala Ile Ser Gly Gln Lys 55 Pro Leu Ile Thr Lys Ala Arg Lys Ser Val Ala Gly Phe Lys Ile Arg Gln Gly Tyr Pro Ile Gly Cys Lys Val Thr Leu Arg Gly Glu Arg Met 85 90 Trp Glu Phe Phe Glu Arg Leu Ile Thr Ile Ala Val Pro Arg Ile Arg 105 100 Asp Phe Arg Gly Leu Ser Ala Lys Ser Phe Asp Gly Arg Gly Asn Tyr 120 Ser Met Gly Val Arg Glu Gln Ile Ile Phe Pro Glu Ile Asp Tyr Asp 135 140 Lys Val Asp Arg Val Arg Gly Leu Asp Ile Thr Ile Thr Thr Ala 150 155 Lys Ser Asp Glu Glu Gly Arg Ala Leu Leu Ala Ala Phe Asp Phe Pro Phe Arg Lys <210> 323 <211> 104 <212> PRT <213> Escherichia coli Met Ala Ala Lys Ile Arg Arg Asp Asp Glu Val Ile Val Leu Thr Gly 10 Lys Asp Lys Gly Lys Arg Gly Lys Val Lys Asn Val Leu Ser Ser Gly 25 Lys Val Ile Val Glu Gly Ile Asn Leu Val Lys Lys His Gln Lys Pro Val Pro Ala Leu Asn Gln Pro Gly Gly Ile Val Glu Lys Glu Ala Ala 55 Ile Gln Val Ser Asn Val Ala Ile Phe Asn Ala Ala Thr Gly Lys Ala 70 75 Asp Arg Val Gly Phe Arg Phe Glu Asp Gly Lys Lys Val Arg Phe Phe 85 Lys Ser Asn Ser Glu Thr Ile Lys 100 <210> 324 <211> 123 <212> PRT <213> Escherichia coli

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Ser Ala Gly Ile Asn Ala Ala Ser Pro Asn Lys Glu Leu Ala Lys Glu
                       295
Phe Leu Glu Asn Tyr Leu Leu Thr Asp Glu Gly Leu Glu Ala Val Asn
                   310
                                       315
Lys Asp Lys Pro Leu Gly Ala Val Ala Leu Lys Ser Tyr Glu Glu Glu
               325
                                  330
Leu Ala Lys Asp Pro Arg Ile Ala Ala Thr Met Glu Asn Ala Gln Lys
                               345
Gly Glu Ile Met Pro Asn Ile Pro Gln Met Ser Ala Phe Trp Tyr Ala
                          360
Val Arg Thr Ala Val Ile Asn Ala Ala Ser Gly Arg Gln Thr Val Asp
                      375
Glu Ala Leu Lys Asp Ala Gln Thr Arg Ile Thr Lys
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<211> 514
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<213> Escherichia coli
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Trp Ser Val Leu Gly Leu Leu Gly Leu Leu Val Gly Tyr Leu Val Val
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Leu Met Tyr Ala Gln Gly Glu Tyr Leu Phe Ala Ile Thr Thr Leu Ile
                           40
Leu Ser Ser Ala Gly Leu Tyr Ile Phe Ala Asn Arg Lys Ala Tyr Ala
Trp Arg Tyr Val Tyr Pro Gly Met Ala Gly Met Gly Leu Phe Val Leu
                   70
Phe Pro Leu Val Cys Thr Ile Ala Ile Ala Phe Thr Asn Tyr Ser Ser
              8.5
                                  90
Thr Asn Gln Leu Thr Phe Glu Arg Ala Gln Glu Val Leu Leu Asp Arg
                              105
Ser Trp Gln Ala Gly Lys Thr Tyr Asn Phe Gly Leu Tyr Pro Ala Gly
                          120
Asp Glu Trp Gln Leu Ala Leu Ser Asp Gly Glu Thr Gly Lys Asn Tyr
             135
                                          140
Leu Ser Asp Ala Phe Lys Phe Gly Gly Glu Gln Lys Leu Gln Leu Lys
           150
                                      155
Glu Thr Thr Ala Gln Pro Glu Gly Glu Arg Ala Asn Leu Arg Val Ile
                                  170
Thr Gln Asn Arg Gln Ala Leu Ser Asp Ile Thr Ala Ile Leu Pro Asp
           180
                               185
Gly Asn Lys Val Met Met Ser Ser Leu Arg Gln Phe Ser Gly Thr Gln
      195
                          200
Pro Leu Tyr Thr Leu Asp Gly Asp Gly Thr Leu Thr Asn Asn Gln Ser
                      215
                                           220
Gly Val Lys Tyr Arg Pro Asn Asn Gln Ile Gly Phe Tyr Gln Ser Ile
                  230
                                      235
Thr Ala Asp Gly Asn Trp Gly Asp Glu Lys Leu Ser Pro Gly Tyr Thr
              245
                                   250
Val Thr Thr Gly Trp Lys Asn Phe Thr Arg Val Phe Thr Asp Glu Gly
           260
                               265
Ile Gln Lys Pro Phe Leu Ala Ile Phe Val Trp Thr Val Val Phe Ser
                          280
Leu Ile Thr Val Phe Leu Thr Val Ala Val Gly Met Val Leu Ala Cys
                       295
                                           300
Leu Val Gln Trp Glu Ala Leu Arg Gly Lys Ala Val Tyr Arg Val Leu
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310
                                       315
Leu Ile Leu Pro Tyr Ala Val Pro Ser Phe Ile Ser Ile Leu Ile Phe
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             325
Lys Gly Leu Phe Asn Gln Ser Phe Gly Glu Ile Asn Met Met Leu Ser
                               345
Ala Leu Phe Gly Val Lys Pro Ala Trp Phe Ser Asp Pro Thr Thr Ala
                           360
Arg Thr Met Leu Ile Ile Val Asn Thr Trp Leu Gly Tyr Pro Tyr Met
                       375
                                           380
Met Ile Leu Cys Met Gly Leu Leu Lys Ala Ile Pro Asp Asp Leu Tyr
                   390
                                       395
Glu Ala Ser Ala Met Asp Gly Ala Gly Pro Phe Gln Asn Phe Phe Lys
                                   410
Ile Thr Leu Pro Leu Leu Ile Lys Pro Leu Thr Pro Leu Met Ile Ala
                               425
Ser Phe Ala Phe Asn Phe Asn Asn Phe Val Leu Ile Gln Leu Leu Thr
                           440
Asn Gly Gly Pro Asp Arg Leu Gly Thr Thr Thr Pro Ala Gly Tyr Thr
                       455
                                          460
Asp Leu Leu Val Asn Tyr Thr Tyr Arg Ile Ala Phe Glu Gly Gly
                  470
Gly Gln Asp Phe Gly Leu Ala Ala Ala Ile Ala Thr Leu Ile Phe Leu
               485
                                  490
Leu Val Gly Ala Leu Ala Ile Val Asn Leu Lys Ala Thr Arg Met Lys
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Phe Asp
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<211> 296

<212> PRT

<213> Escherichia coli

<400> 327

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Pro Leu Ser Val Pro Ile Leu Ala Val Phe Ile Leu Ser Phe Ile 215 Ala Ala Ile Thr Glu Val Pro Val Ala Ser Leu Leu Leu Arg Asp Val 230 235 Asn Ser Tyr Thr Leu Ala Val Gly Met Gln Gln Tyr Leu Asn Pro Gln 245 250 Asn Tyr Leu Trp Gly Asp Phe Ala Ala Ala Ala Val Met Ser Ala Leu 260 265 Pro Ile Thr Ile Val Phe Leu Leu Ala Gln Arg Trp Leu Val Asn Gly 280 275 Leu Thr Ala Gly Gly Val Lys Gly <210> 328 <211> 673 <212> PRT <213> Escherichia coli <400> 328 Met Arg Leu Asn Pro Gly Gln Gln Ala Val Glu Phe Val Thr Gly 1 10 Pro Cys Leu Val Leu Ala Gly Ala Gly Ser Gly Lys Thr Arg Val Ile 25 Thr Asn Lys Ile Ala His Leu Ile Arg Gly Cys Gly Tyr Gln Ala Arg His Ile Ala Ala Val Thr Phe Thr Asn Lys Ala Ala Arg Glu Met Lys 55 60 Glu Arg Val Gly Gln Thr Leu Gly Arg Lys Glu Ala Arg Gly Leu Met 70 75 Ile Ser Thr Phe His Thr Leu Gly Leu Asp Ile Ile Lys Arg Glu Tyr 85 90 Ala Ala Leu Gly Met Lys Ala Asn Phe Ser Leu Phe Asp Asp Thr Asp 100 105 Gln Leu Ala Leu Leu Lys Glu Leu Thr Glu Gly Leu Ile Glu Asp Asp 120 Lys Val Leu Leu Gln Gln Leu Ile Ser Thr Ile Ser Asn Trp Lys Asn 135 140 Asp Leu Lys Thr Pro Ser Gln Ala Ala Ala Ser Ala Ile Gly Glu Arg 155 150 Asp Arg Ile Phe Ala His Cys Tyr Gly Leu Tyr Asp Ala His Leu Lys 170 Ala Cys Asn Val Leu Asp Phe Asp Asp Leu Ile Leu Leu Pro Thr Leu 185 Leu Leu Gln Ala Asn Glu Glu Val Arg Lys Arg Trp Gln Asn Lys Ile 200 Arg Tyr Leu Leu Val Asp Glu Tyr Gln Asp Thr Asn Thr Ser Gln Tyr 215 Glu Leu Val Lys Leu Leu Val Gly Ser Arg Ala Arg Phe Thr Val Val 230 235 Gly Asp Asp Asp Gln Ser Ile Tyr Ser Trp Arg Gly Ala Arg Pro Gln 250 245 Asn Leu Val Leu Leu Ser Gln Asp Phe Pro Ala Leu Lys Val Ile Lys 265 Leu Glu Gln Asn Tyr Arg Ser Ser Gly Arg Ile Leu Lys Ala Ala Asn 280 Ile Leu Ile Ala Asn Asn Pro His Val Phe Glu Lys Arg Leu Phe Ser 300 295 Glu Leu Gly Tyr Gly Ala Glu Leu Lys Val Leu Ser Ala Asn Asn Glu 310 315 Glu His Glu Ala Glu Arg Val Thr Gly Glu Leu Ile Ala His His Phe

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330
Val Asn Lys Thr Gln Tyr Lys Asp Tyr Ala Ile Leu Tyr Arg Gly Asn
                     345
          340
His Gln Ser Arg Val Phe Glu Lys Phe Leu Met Gln Asn Arg Ile Pro
                       360
Tyr Lys Ile Ser Gly Gly Thr Ser Phe Phe Ser Arg Pro Glu Ile Lys
                  375
Asp Leu Leu Ala Tyr Leu Arg Val Leu Thr Asn Pro Asp Asp Asp Ser
        390
                         .395
Ala Phe Leu Arg Ile Val Asn Thr Pro Lys Arg Glu Ile Gly Pro Ala
       405 410
Thr Leu Lys Lys Leu Gly Glu Trp Ala Met Thr Arg Asn Lys Ser Met
         420
                           425
Phe Thr Ala Ser Phe Asp Met Gly Leu Ser Gln Thr Leu Ser Gly Arg
                        440
Gly Tyr Glu Ala Leu Thr Arg Phe Thr His Trp Leu Ala Glu Ile Gln
                    455
                                       460
Arg Leu Ala Glu Arg Glu Pro Ile Ala Ala Val Arg Asp Leu Ile His
                                  475
                 470
Gly Met Asp Tyr Glu Ser Trp Leu Tyr Glu Thr Ser Pro Ser Pro Lys
             485
                               490
Ala Ala Glu Met Arg Met Lys Asn Val Asn Gln Leu Phe Ser Trp Met
                            505
Thr Glu Met Leu Glu Gly Ser Glu Leu Asp Glu Pro Met Thr Leu Thr
                      520
                                         525
Gln Val Val Thr Arg Phe Thr Leu Arg Asp Met Met Glu Arg Gly Glu
                    535
                                       540
Ser Glu Glu Glu Leu Asp Gln Val Gln Leu Met Thr Leu His Ala Ser
                                   555
                 550
Lys Gly Leu Glu Phe Pro Tyr Val Tyr Met Val Gly Met Glu Gly
                               570
             565
Phe Leu Pro His Gln Ser Ser Ile Asp Glu Asp Asn Ile Asp Glu Glu
         580
                           585
Arg Arg Leu Ala Tyr Val Gly Ile Thr Arg Ala Gln Lys Glu Leu Thr
                        600
Phe Thr Leu Cys Lys Glu Arg Arg Gln Tyr Gly Glu Leu Val Arg Pro
                                      620
                    615
Glu Pro Ser Arg Phe Leu Leu Glu Leu Pro Gln Asp Asp Leu Ile Trp
              630 635
Glu Gln Glu Arg Lys Val Val Ser Ala Glu Glu Arg Met Gln Lys Gly
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Gln Ser His Leu Ala Asn Leu Lys Ala Met Met Ala Ala Lys Arg Gly
Lys
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<210> 329

<211> 403

<212> PRT

<213> Escherichia coli

<400> 329

 Met
 Wal
 Thr
 Val
 Val
 Ser
 Asn
 Tyr
 Cys
 Gln
 Leu
 Ser
 Gln
 Thr
 Gln

 Leu
 Ser
 Gln
 Thr
 Phe
 Ala
 Glu
 Lys
 Phe
 Thr
 Val
 Thr
 Glu
 Glu
 Leu
 Leu
 Leu
 Ala
 Leu
 Ser
 Gly
 Asp
 Glu
 Glu
 Ser
 Ile
 Glu
 Ala

 Leu
 Leu
 His
 Asn
 Ile
 Ala
 Leu
 Gly
 Tyr
 Asp
 Lys
 Phe
 Gly
 Ala

 50
 Fragge
 <td

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Glu Asp Ile Leu Tyr His Ile Val Arg Thr Pro Thr Asn Glu Thr Leu
                   70
                                       75
Ser Ile Ile Arg Leu Ile Lys Asn Ala Cys Leu Lys Leu Tyr Asn Leu
Ala His Ile Ala Thr Asn Ser Pro Leu Lys Ser His Asp Ser Asp Asp
                               105
Leu Leu Phe Lys Lys Leu Phe Ser Pro Ser Lys Leu Met Thr Ile Ile
                           120
Gly Asp Glu Ile Pro Leu Ile Ser Glu Lys Gln Ser Leu Ser Lys Val
                   135
Leu Leu Asn Asp Glu Asn Asn Glu Leu Ser Asp Gly Thr Asn Phe Trp
                  150
Asp Lys Asn Arg Gln Leu Thr Thr Asp Glu Ile Ala Cys Tyr Leu Gln
              165
                                  170
Lys Ile Ala Ala Asn Ala Lys Asn Thr Gln Val Asn Tyr Pro Thr Gly
                              185
          180
Leu Tyr Val Pro Tyr Ser Thr Arg Thr His Leu Glu Asp Ala Leu Asn
                           200
       195
Glu Asn Ile Lys Ser Asp Pro Ser Trp Pro Asn Glu Val Gln Leu Phe
                       215
                                           220
Pro Ile Asn Thr Gly Gly His Trp Ile Leu Val Ser Leu Gln Lys Ile
                                       235
                   230
Val Asn Lys Lys Asn Asn Lys Leu Gln Ile Lys Cys Val Ile Phe Asn
                                   250
Ser Leu Arg Ala Leu Gly Tyr Asp Lys Glu Asn Ser Leu Lys Arg Val
                               265
                                                   270
Ile Asn Ser Phe Asn Ser Glu Leu Met Gly Glu Met Ser Asn Asn Asn
                           280
                                               285
Ile Lys Val His Leu Asn Glu Pro Glu Ile Ile Phe Leu His Ala Asp
                      295
                                           300
Leu Gln Gln Tyr Leu Ser Gln Ser Cys Gly Ala Phe Val Cys Met Ala
                                       315
                   310
Ala Gln Glu Val Ile Glu Gln Arg Glu Ser Asn Ser Asp Ser Ala Pro
               325
                                   330
Tyr Thr Leu Leu Lys Asn His Ala Asp Arg Phe Lys Lys Tyr Ser Ala
                               345
           340
Glu Glu Gln Tyr Glu Ile Asp Phe Gln His Arg Leu Ala Asn Arg Asn
                           360
       355
Cys Tyr Leu Asp Lys Tyr Gly Asp Ala Asn Ile Asn His Tyr Tyr Arg
                       375
                                           380
Asn Leu Glu Ile Lys His Ser Gln Pro Lys Asn Arg Ala Ser Gly Lys
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Arg Val Ser
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<210> 330

<211> 296

<212> PRT

<213> Escherichia coli

<400> 330

 Met
 Met
 Phe
 Lys
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 Tyr
 Leu
 Gln
 Val
 Thr
 Lys
 Pro
 Gly
 Ile
 Ile
 Ile
 Jhe

 Gly
 Asn
 Leu
 Ile
 Ser
 Val
 Ile
 Gly
 Gly
 Phe
 Leu
 Leu
 Leu
 Ala
 Ser
 Lys
 Gly

 Ser
 Ile
 Asp
 Tyr
 Pro
 Leu
 Phe
 Ile
 Tyr
 Thr
 Leu
 Val
 Gly
 Val
 Ser
 Leu

 Val
 Val
 Ala
 Ser
 Gly
 Cys
 Val
 Phe
 Asn
 Asn
 Tyr
 Ile
 Asp
 Arg
 Arg
 Asp
 Arg
 Val
 Leu
 V

```
70
Ile Ser Pro Ala Val Ser Leu Val Tyr Ala Thr Leu Leu Gly Ile Ala
              85
Gly Phe Met Leu Leu Trp Phe Gly Ala Asn Pro Leu Ala Cys Trp Leu
                             105
Gly Val Met Gly Phe Val Val Tyr Val Gly Val Tyr Ser Leu Tyr Met
                         120
Lys Arg His Ser Val Tyr Gly Thr Leu Ile Gly Ser Leu Ser Gly Ala
            135
                                         140
Ala Pro Pro Val Ile Gly Tyr Cys Ala Val Thr Gly Glu Phe Asp Ser
         150
                                     155
Gly Ala Ala Ile Leu Leu Ala Ile Phe Ser Leu Trp Gln Met Pro His
                                  170
Ser Tyr Ala Ile Ala Ile Phe Arg Phe Lys Asp Tyr Gln Ala Ala Asn
                              185
Ile Pro Val Leu Pro Val Val Lys Gly Ile Ser Val Ala Lys Asn His
                          200
Ile Thr Leu Tyr Ile Ile Ala Phe Ala Val Ala Thr Leu Met Leu Ser
                       215
                                          220
Leu Gly Gly Tyr Ala Gly Tyr Lys Tyr Leu Val Val Ala Ala Ala Val
                   230
                                     235
Ser Val Trp Trp Leu Gly Met Ala Leu Arg Gly Tyr Lys Val Ala Asp
                                 250
              245
Asp Arg Ile Trp Ala Arg Lys Leu Phe Gly Phe Ser Ile Ile Ala Ile
                           265
          260
Thr Ala Leu Ser Val Met Met Ser Val Asp Phe Met Val Pro Asp Ser
                          280
    275
His Thr Leu Leu Ala Ala Val Trp
<210> 331
<211> 315
<212> PRT
<213> Escherichia coli
<400> 331
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Ala Gly Thr Val Leu Leu Ser Gly Cys Asn Ser Ala Leu Leu Asp Pro
                              25
Lys Gly Gln Ile Gly Leu Glu Gln Arg Ser Leu Ile Leu Thr Ala Phe
                          40
Gly Leu Met Leu Ile Val Val Ile Pro Ala Ile Leu Met Ala Val Gly
                      55
Phe Ala Trp Lys Tyr Arg Ala Ser Asn Lys Asp Ala Lys Tyr Ser Pro
                                      75
                   70
Asn Trp Ser His Ser Asn Lys Val Glu Ala Val Val Trp Thr Val Pro
                                  90
               85
Ile Leu Ile Ile Ile Phe Leu Ala Val Leu Thr Trp Lys Thr Thr His
                              105
           100
Ala Leu Glu Pro Ser Lys Pro Leu Ala His Asp Glu Lys Pro Ile Thr
                                             125
                          120
Ile Glu Val Val Ser Met Asp Trp Lys Trp Phe Phe Ile Tyr Pro Glu
                      135
                                         140
Gln Gly Ile Ala Thr Val Asn Glu Ile Ala Phe Pro Ala Asn Thr Pro
                                     155
                  150
Val Tyr Phe Lys Val Thr Ser Asn Ser Val Met Asn Ser Phe Phe Ile
                                 170
              165
Pro Arg Leu Gly Ser Gln Ile Tyr Ala Met Ala Gly Met Gln Thr Arg
                        . 185
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Leu His Leu Ile Ala Asn Glu Pro Gly Thr Tyr Asp Gly Ile Ser Ala 200 195 Ser Tyr Ser Gly Pro Gly Phe Ser Gly Met Lys Phe Lys Ala Ile Ala 215 220 Thr Pro Asp Arg Ala Ala Phe Asp Gln Trp Val Ala Lys Ala Lys Gln 230 235 Ser Pro Asn Thr Met Ser Asp Met Ala Ala Phe Glu Lys Leu Ala Ala 250 245 Pro Ser Glu Tyr Asn Gln Val Glu Tyr Phe Ser Asn Val Lys Pro Asp 265 260 Leu Phe Ala Asp Val Ile Asn Lys Phe Met Ala His Gly Lys Ser Met 280 Asp Met Thr Gln Pro Glu Gly Glu His Ser Ala His Glu Gly Met Glu 295 300 Gly Met Asp Met Ser His Ala Glu Ser Ala His <210> 332 <211> 663 <212> PRT <213> Escherichia coli <400> 332 Met Phe Gly Lys Leu Ser Leu Asp Ala Val Pro Phe His Glu Pro Ile 10 Val Met Val Thr Ile Ala Gly Ile Ile Leu Gly Gly Leu Ala Leu Val 25 Gly Leu Ile Thr Tyr Phe Gly Lys Trp Thr Tyr Leu Trp Lys Glu Trp 40 Leu Thr Ser Val Asp His Lys Arg Leu Gly Ile Met Tyr Ile Ile Val Ala Ile Val Met Leu Leu Arg Gly Phe Ala Asp Ala Ile Met Met Arg 70 Ser Gln Gln Ala Leu Ala Ser Ala Gly Glu Ala Gly Phe Leu Pro Pro 90 His His Tyr Asp Gln Ile Phe Thr Ala His Gly Val Ile Met Ile Phe 100 105 Phe Val Ala Met Pro Phe Val Ile Gly Leu Met Asn Leu Val Val Pro 120 Leu Gln Ile Gly Ala Arg Asp Val Ala Phe Pro Phe Leu Asn Asn Leu 135 140 Ser Phe Trp Phe Thr Val Val Gly Val Ile Leu Val Asn Val Ser Leu 150 155 Gly Val Gly Glu Phe Ala Gln Thr Gly Trp Leu Ala Tyr Pro Pro Leu 170 165 Ser Gly Ile Glu Tyr Ser Pro Gly Val Gly Val Asp Tyr Trp Ile Trp 185 190 Ser Leu Gln Leu Ser Gly Ile Gly Thr Thr Leu Thr Gly Ile Asn Phe 200 205 195 Phe Val Thr Ile Leu Lys Met Arg Ala Pro Gly Met Thr Met Phe Lys 215 220 Met Pro Val Phe Thr Trp Ala Ser Leu Cys Ala Asn Val Leu Ile Ile 235 230 Ala Ser Phe Pro Ile Leu Thr Val Thr Val Ala Leu Leu Thr Leu Asp 245 250 Arg Tyr Leu Gly Thr His Phe Phe Thr Asn Asp Met Gly Gly Asn Met 265 270 260 Met Met Tyr Ile Asn Leu Ile Trp Ala Trp Gly His Pro Glu Val Tyr 280 285 275 Ile Leu Ile Leu Pro Val Phe Gly Val Phe Ser Glu Ile Ala Ala Thr

```
295
Phe Ser Arg Lys Arg Leu Phe Gly Tyr Thr Ser Leu Val Trp Ala Thr
                  310
                                     315
Val Cys Ile Thr Val Leu Ser Phe Ile Val Trp Leu His His Phe Phe
              325
                                  330
Thr Met Gly Ala Gly Ala Asn Val Asn Ala Phe Phe Gly Ile Thr Thr
           340
                              345
Met Ile Ile Ala Ile Pro Thr Gly Val Lys Ile Phe Asn Trp Leu Phe
                        360
Thr Met Tyr Gln Gly Arg Ile Val Phe His Ser Ala Met Leu Trp Thr
                       375
                                          380
Ile Gly Phe Ile Val Thr Phe Ser Val Gly Gly Met Thr Gly Val Leu
                   390
                                      395
Leu Ala Val Pro Gly Ala Asp Phe Val Leu His Asn Ser Leu Phe Leu
              405
                                   410
Ile Ala His Phe His Asn Val Ile Ile Gly Gly Val Val Phe Gly Cys
                              425
           420
Phe Ala Gly Met Thr Tyr Trp Trp Pro Lys Ala Phe Gly Phe Lys Leu
                         440
Asn Glu Thr Trp Gly Lys Arg Ala Phe Trp Phe Trp Ile Ile Gly Phe
                      455
                                          460
Phe Val Ala Phe Met Pro Leu Tyr Ala Leu Gly Phe Met Gly Met Thr
                  470
                                    475
Arg Arg Leu Ser Gln Gln Ile Asp Pro Gln Phe His Thr Met Leu Met
              485
                                  490
Ile Ala Ala Ser Gly Ala Val Leu Ile Ala Leu Gly Ile Leu Cys Leu
           500
                               505
Val Ile Gln Met Tyr Val Ser Ile Arg Asp Arg Asp Gln Asn Arg Asp
                          520
Leu Thr Gly Asp Pro Trp Gly Gly Arg Thr Leu Glu Trp Ala Thr Ser
                      535
                                         540
Ser Pro Pro Pro Phe Tyr Asn Phe Ala Val Val Pro His Val His Glu
                550
                               555
Arg Asp Ala Phe Trp Glu Met Lys Glu Lys Gly Glu Ala Tyr Lys Lys
              565
                     570
Pro Asp His Tyr Glu Glu Ile His Met Pro Lys Asn Ser Gly Ala Gly
                              585
Ile Val Ile Ala Ala Phe Ser Thr Ile Phe Gly Phe Ala Met Ile Trp
                        600
His Ile Trp Trp Leu Ala Ile Val Gly Phe Ala Gly Met Ile Ile Thr
                       615
Trp Ile Val Lys Ser Phe Asp Glu Asp Val Asp Tyr Tyr Val Pro Val
                   630
                                      635
Ala Glu Ile Glu Lys Leu Glu Asn Gln His Phe Asp Glu Ile Thr Lys
               645
                                   650
Ala Gly Leu Lys Asn Gly Asn
           660
<210> 333
<211> 204
<212> PRT
<213> Escherichia coli
<400> 333
Met Ala Thr Asp Thr Leu Thr His Ala Thr Ala His Ala His Glu His
                                  10
Gly His His Asp Ala Gly Gly Thr Lys Ile Phe Gly Phe Trp Ile Tyr
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20 25 30
Leu Met Ser Asp Cys Ile Leu Phe Ser Ile Leu Phe Ala Thr Tyr Ala
35 40 45

```
Val Leu Val Asn Gly Thr Ala Gly Gly Pro Thr Gly Lys Asp Ile Phe
                       55
Glu Leu Pro Phe Val Leu Val Glu Thr Phe Leu Leu Phe Ser Ser
                                        75
Ile Thr Tyr Gly Met Ala Ala Ile Ala Met Tyr Lys Asn Asn Lys Ser
Gln Val Ile Ser Trp Leu Ala Leu Thr Trp Leu Phe Gly Ala Gly Phe
           100
                                105
Ile Gly Met Glu Ile Tyr Glu Phe His His Leu Ile Val Asn Gly Met
       115
                           120
Gly Pro Asp Arg Ser Gly Phe Leu Ser Ala Phe Phe Ala Leu Val Gly
                       135
                                           140
Thr His Gly Leu His Val Thr Ser Gly Leu Ile Trp Met Ala Val Leu
                   150
                                       155
Met Val Gln Ile Ala Arg Arg Gly Leu Thr Ser Thr Asn Arg Thr Arg
               165
                                  170
Ile Met Cys Leu Ser Leu Phe Trp His Phe Leu Asp Val Val Trp Ile
                               185
Cys Val Phe Thr Val Val Tyr Leu Met Gly Ala Met
                            200
<210> 334
<211> 109
<212> PRT
<213> Escherichia coli
<400> 334
Met Ser His Ser Thr Asp His Ser Gly Ala Ser His Gly Ser Val Lys
                                    10
Thr Tyr Met Thr Gly Phe Ile Leu Ser Ile Ile Leu Thr Val Ile Pro
                                25
Phe Trp Met Val Met Thr Gly Ala Ala Ser Pro Ala Val Ile Leu Gly
Thr Ile Leu Ala Met Ala Val Val Gln Val Leu Val His Leu Val Cys
Phe Leu His Met Asn Thr Lys Ser Asp Glu Gly Trp Asn Met Thr Ala
                   70
Phe Val Phe Thr Val Leu Ile Ile Ala Ile Leu Val Val Gly Ser Ile
Trp Ile Met Trp Asn Leu Asn Tyr Asn Met Met His
<210> 335
<211> 587
<212> PRT
<213> Escherichia coli
<400> 335
Met Gln Trp Gln Thr Lys Leu Pro Leu Ile Ala Ile Leu Arg Gly Ile
1
Thr Pro Asp Glu Ala Leu Ala His Val Gly Ala Val Ile Asp Ala Gly
                                25
            20
Phe Asp Ala Val Glu Ile Pro Leu Asn Ser Pro Gln Trp Glu Gln Ser
Ile Pro Ala Ile Val Asp Ala Tyr Gly Asp Lys Ala Leu Ile Gly Ala
Gly Thr Val Leu Lys Pro Glu Gln Val Asp Ala Leu Ala Arg Met Gly
                   70
                                        75
Cys Gln Leu Ile Val Thr Pro Asn Ile His Ser Glu Val Ile Arg Arg
                85
                                    90
```

Ala	Val	Gly	Tyr 100	Gly	Met	Thr	Val	Cys 105	Pro	Gly	Cys	Ala	Thr 110	Ala	Thr
Glu	Ala	Phe 115	Thr	Ala	Leu	Glu	Ala 120	Gly	Ala	Ala	Gly	Ala 125	Glu	Asn	Ile
Ser	Val 130	Ile	Gly	Phe	Trp	Ser 135	Ala	Ile	His	Gln	Ser 140	Val	Lys	Ser	Gly
Ile 145	Ala	Ile	Gly	His	Arg 150	Ser	Leu	Cys	Arg	Trp 155	Arg	Arg	Asp	Ala	Glu 160
Asn	Leu	Ala	Gln	Trp 165	Ile	Asp	Ala	Gly	Cys 170	Ala	Gly	Ala	Gly	Leu 175	Gly
	_		Tyr 180					185					190		
		195	Phe				200					205			
Thr	Lys 210	Ile	Thr	Thr	Tyr	Arg 215	Leu	Pro	Pro	Arg	Trp 220	Met	Phe	Leu	Lys
225			Asp		230			_		235					240
_	_		Arg	245					250					255	
		_	Gln 260					265					270		
-	-	275	Gly				280			•		285			
	290		Asp			295					300				
305			Trp		310					315	_				320
	_		Trp	325					330					335	
	_		Leu 340					345					350		
		355	Leu	•			360					365			
	370		Val			375					380				
385			Asp		390					395					400
			Glu	405					410					415	•
			Glu 420					425					430		
		435					440					445			
	450		Leu			455					460				
465			Gly		470					475					480
			Asp	485					490					495	
			Ala 500					505					510		
		515	Gln				520					525			
	530		Val			535					540				
545			Leu		550					555					560
Lys	Val	Ile	Glu	Phe 565	Ser	Lys	Asn	Ala	Pro 570	Asp	Trp	Arg	Asn	Pro 575	Leu

Trp Arg His Glu Asp Asn Ser Val Ala Glu Trp <210> 336 <211> 292 <212> PRT <213> Escherichia coli <400> 336 Met Thr Ala Arg Tyr Ile Ala Ile Asp Trp Gly Ser Thr Asn Leu Arg Ala Trp Leu Tyr Gln Gly Asp His Cys Leu Glu Ser Arg Gln Ser Glu 25 Ala Gly Val Thr Arg Leu Asn Gly Lys Ser Pro Ala Ala Val Leu Ala 40 Glu Val Thr Thr Asp Trp Arg Glu Glu Lys Thr Pro Val Val Met Ala Gly Met Val Gly Ser Asn Val Gly Trp Lys Val Ala Pro Tyr Leu Ser 70 Val Pro Ala Cys Phe Ser Ser Ile Gly Glu Gln Leu Thr Ser Val Gly 90 Asp Asn Ile Trp Ile Ile Pro Gly Leu Cys Val Ser His Asp Asn 105 His Asn Val Met Arg Gly Glu Glu Thr Gln Leu Ile Gly Ala Arg Ala 120 Leu Ala Pro Ser Ser Leu Tyr Val Met Pro Gly Thr His Cys Lys Trp 130 135 140 Val Gln Ala Asp Ser Gln Gln Ile Asn Asp Phe Arg Thr Val Met Thr 150 155 Gly Glu Leu His His Leu Leu Leu Asn His Ser Leu Ile Gly Ala Gly 165 170 Leu Pro Pro Gln Glu Asn Ser Ala Asp Ala Phe Thr Ala Gly Leu Glu 185 Arg Gly Leu Asn Thr Pro Ala Ile Leu Pro Gln Leu Phe Glu Val Arg 195 200 205 Ala Ser His Val Leu Gly Thr Leu Pro Arg Glu Gln Val Ser Glu Phe 215 220 Leu Ser Gly Leu Leu Ile Gly Ala Glu Val Ala Ser Met Arg Asp Tyr 230 Val Ala His Gln His Ala Ile Thr Leu Val Ala Gly Thr Ser Leu Thr 250 Ala Arg Tyr Gln Gln Ala Phe Gln Ala Met Gly Cys Asp Val Thr Ala 265 Val Ala Gly Asp Thr Ala Phe Gln Ala Gly Ile Arg Ser Ile Ala His Ala Val Ala Asn 290 <210> 337 <211> 128 <212> PRT <213> Escherichia coli <400> 337 Met Thr Leu Asn Lys Thr Asp Arg Ile Val Ile Thr Leu Gly Lys Gln 10 Ile Val His Gly Lys Tyr Val Pro Gly Ser Pro Leu Pro Ala Glu Ala 25 Glu Leu Cys Glu Glu Phe Ala Thr Ser Arg Asn Ile Ile Arg Glu Val

```
Phe Arg Ser Leu Met Ala Lys Arg Leu Ile Glu Met Lys Arg Tyr Arg
                  55
Gly Ala Phe Val Ala Pro Arg Asn Gln Trp Asn Tyr Leu Asp Thr Asp
               70
Val Leu Gln Trp Val Leu Glu Asn Asp Tyr Asp Pro Arg Leu Ile Ser
                                90
Ala Met Ser Glu Val Arg Asn Leu Val Glu Pro Ala Ile Ala Arg Trp
                      105 110
Glu Gln Ser Ala Arg Leu Pro Ala Ile Trp Arg Arg Leu Asn Arg Arg
       115 120
<210> 338
<211> 98
<212> PRT
<213> Escherichia coli
<400> 338
Met Ile Ala Asn Asn Gln Asp Arg Glu Ala Phe Asn Glu Ala Asp Ile
                                 10
1
Arg Tyr His Glu Ala Val Leu Gln Ser Val His Asn Pro Val Leu Gln
        20
                             25
Gln Leu Ser Ile Ala Ile Ser Ser Leu Gln Arg Ala Val Phe Glu Arg
                                            45
                          40
Thr Trp Met Gly Asp Glu Ala Asn Met Pro Gln Thr Leu Gln Glu His
                                        60
                     55
Lys Ala Leu Phe Asp Ala Ile Arg His Gln Asp Gly Asp Ala Ala Glu
65 70
Gln Ala Ala Leu Thr Met Ile Ala Ser Ser Thr Arg Arg Leu Lys Glu
                                 90
Ile Thr
<210> 339
<211> 118
<212> PRT
<213> Escherichia coli
<400> 339
Met Ala Arg Val Lys Arg Gly Val Ile Ala Arg Ala Arg His Lys Lys
                                 10
Ile Leu Lys Gln Ala Lys Gly Tyr Tyr Gly Ala Arg Ser Arg Val Tyr
                             25 .
Arg Val Ala Phe Gln Ala Val Ile Lys Ala Gly Gln Tyr Ala Tyr Arg
                          40
                                           45
Asp Arg Arg Gln Arg Lys Arg Gln Phe Arg Gln Leu Trp Ile Ala Arg
                      55
Ile Asn Ala Ala Ala Arg Gln Asn Gly Ile Ser Tyr Ser Lys Phe Ile
                 70
Asn Gly Leu Lys Lys Ala Ser Val Glu Ile Asp Arg Lys Ile Leu Ala
              85
                                 90
Asp Ile Ala Val Phe Asp Lys Val Ala Phe Thr Ala Leu Val Glu Lys
                             105
           100
Ala Lys Ala Ala Leu Ala
<210> 340
<211> 65
<212> PRT
<213> Escherichia coli
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Met Pro Lys Ile Lys Thr Val Arg Gly Ala Ala Lys Arg Phe Lys Lys
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Thr Gly Lys Gly Gly Phe Lys His Lys His Ala Asn Leu Arg His Ile
Leu Thr Lys Lys Ala Thr Lys Arg Lys Arg His Leu Arg Pro Lys Ala
                           40
Met Val Ser Lys Gly Asp Leu Gly Leu Val Ile Ala Cys Leu Pro Tyr
Ala
65
<210> 341
<211> 180
<212> PRT
<213> Escherichia coli
<400> 341
Met Lys Gly Gly Lys Arg Val Gln Thr Ala Arg Pro Asn Arg Ile Asn
                                   10
Gly Glu Ile Arg Ala Gln Glu Val Arg Leu Thr Gly Leu Glu Gly Glu
                               25
Gln Leu Gly Ile Val Ser Leu Arg Glu Ala Leu Glu Lys Ala Glu Glu
       35
Ala Gly Val Asp Leu Val Glu Ile Ser Pro Asn Ala Glu Pro Pro Val
Cys Arg Ile Met Asp Tyr Gly Lys Phe Leu Tyr Glu Lys Ser Lys Ser
                   70
                                      75
Ser Lys Glu Gln Lys Lys Gln Lys Val Ile Gln Val Lys Glu Ile
               85
                                  90
Lys Phe Arg Pro Gly Thr Asp Glu Gly Asp Tyr Gln Val Lys Leu Arg
                               105
           100
                                                  110
Ser Leu Ile Arg Phe Leu Glu Glu Gly Asp Lys Ala Lys Ile Thr Leu
                           120
                                               125
Arg Phe Arg Gly Arg Glu Met Ala His Gln Gln Ile Gly Met Glu Val
                       135
                                           140
Leu Asn Arg Val Lys Asp Asp Leu Gln Glu Leu Ala Val Val Glu Ser
                  150
                                      155
Phe Pro Thr Lys Ile Glu Gly Arg Gln Met Ile Met Val Leu Ala Pro
Lys Lys Lys Gln
            180
<210> 342
<211> 642
<212> PRT
<213> Escherichia coli
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                                   10
1
Ala Val Ser Pro Met Asp Val Ala Leu Asp Ile Gly Pro Gly Leu Ala
                               25
Lys Ala Cys Ile Ala Gly Arg Val Asn Gly Glu Leu Val Asp Ala Cys
Asp Leu Ile Glu Asn Asp Ala Gln Leu Ser Ile Ile Thr Ala Lys Asp
Glu Glu Gly Leu Glu Ile Ile Arg His Ser Cys Ala His Leu Leu Gly
                   70
                                      75
His Ala Ile Lys Gln Leu Trp Pro His Thr Lys Met Ala Ile Gly Pro
```

90 85 Val Ile Asp Asn Gly Phe Tyr Tyr Asp Val Asp Leu Asp Arg Thr Leu 105 Thr Gln Glu Asp Val Glu Ala Leu Glu Lys Arg Met His Glu Leu Ala 120 125 Glu Lys Asn Tyr Asp Val Ile Lys Lys Lys Val Ser Trp His Glu Ala 140 135 Arg Glu Thr Phe Ala Asn Arg Gly Glu Ser Tyr Lys Val Ser Ile Leu 150 155 Asp Glu Asn Ile Ala His Asp Asp Lys Pro Gly Leu Tyr Phe His Glu 165 170 Glu Tyr Val Asp Met Cys Arg Gly Pro His Val Pro Asn Met Arg Phe 185 Cys His His Phe Lys Leu Met Lys Thr Ala Gly Ala Tyr Trp Arg Gly 200 Asp Ser Asn Asn Lys Met Leu Gln Arg Ile Tyr Gly Thr Ala Trp Ala 215 220 Asp Lys Lys Ala Leu Asn Ala Tyr Leu Gln Arg Leu Glu Glu Ala Ala 230 235 Lys Arg Asp His Arg Lys Ile Gly Lys Gln Leu Asp Leu Tyr His Met 250 245 Gln Glu Glu Ala Pro Gly Met Val Phe Trp His Asn Asp Gly Trp Thr 265 260 Ile Phe Arg Glu Leu Glu Val Phe Val Arg Ser Lys Leu Lys Glu Tyr 280 Gln Tyr Gln Glu Val Lys Gly Pro Phe Met Met Asp Arg Val Leu Trp 300 295 Glu Lys Thr Gly His Trp Asp Asn Tyr Lys Asp Ala Met Phe Thr Thr 310 315 Ser Ser Glu Asn Arg Glu Tyr Cys Ile Lys Pro Met Asn Cys Pro Gly 330 325 His Val Gln Ile Phe Asn Gln Gly Leu Lys Ser Tyr Arg Asp Leu Pro 345 Leu Arg Met Ala Glu Phe Gly Ser Cys His Arg Asn Glu Pro Ser Gly 360 Ser Leu His Gly Leu Met Arg Val Arg Gly Phe Thr Gln Asp Asp Ala 375 380 His Ile Phe Cys Thr Glu Glu Gln Ile Arg Asp Glu Val Asn Gly Cys 395 390 Ile Arg Leu Val Tyr Asp Met Tyr Ser Thr Phe Gly Phe Glu Lys Ile 410 405 Val Val Lys Leu Ser Thr Arg Pro Glu Lys Arg Ile Gly Ser Asp Glu 425 Met Trp Asp Arg Ala Glu Ala Asp Leu Ala Val Ala Leu Glu Glu Asn 440 Asn Ile Pro Phe Glu Tyr Gln Leu Gly Glu Gly Ala Phe Tyr Gly Pro 455 Lys Ile Glu Phe Thr Leu Tyr Asp Cys Leu Asp Arg Ala Trp Gln Cys 470 Gly Thr Val Gln Leu Asp Phe Ser Leu Pro Ser Arg Leu Ser Ala Ser 490 Tyr Val Gly Glu Asp Asn Glu Arg Lys Val Pro Val Met Ile His Arg 505 Ala Ile Leu Gly Ser Met Glu Arg Phe Ile Gly Ile Leu Thr Glu Glu 520 Phe Ala Gly Phe Phe Pro Thr Trp Leu Ala Pro Val Gln Val Val Ile 535 540 Met Asn Ile Thr Asp Ser Gln Ser Glu Tyr Val Asn Glu Leu Thr Gln 555 550 Lys Leu Ser Asn Ala Gly Ile Arg Val Lys Ala Asp Leu Arg Asn Glu

570 565 Lys Ile Gly Phe Lys Ile Arg Glu His Thr Leu Arg Arg Val Pro Tyr 585 Met Leu Val Cys Gly Asp Lys Glu Val Glu Ser Gly Lys Val Ala Val 600 Arg Thr Arg Arg Gly Lys Asp Leu Gly Ser Met Asp Val Asn Glu Val 615 620 Ile Glu Lys Leu Gln Gln Glu Ile Arg Ser Arg Ser Leu Lys Gln Leu 630 Glu Glu <210> 343 <211> 330 <212> PRT <213> Escherichia coli <400> 343 Met Lys Ile Lys Asn Ile Leu Leu Thr Leu Cys Thr Ser Leu Leu Leu 10 Thr Asn Val Ala Ala His Ala Lys Glu Val Lys Ile Gly Met Ala Ile Asp Asp Leu Arq Leu Glu Arq Trp Gln Lys Asp Arg Asp Ile Phe Val 40 Lys Lys Ala Glu Ser Leu Gly Ala Lys Val Phe Val Gln Ser Ala Asn 55 Gly Asn Glu Glu Thr Gln Met Ser Gln Ile Glu Asn Met Ile Asn Arg 70 75 Gly Val Asp Val Leu Val Ile Ile Pro Tyr Asn Gly Gln Val Leu Ser 90 85 Asn Val Val Lys Glu Ala Lys Gln Glu Gly Ile Lys Val Leu Ala Tyr 105 Asp Arg Met Ile Asn Asp Ala Asp Ile Asp Phe Tyr Ile Ser Phe Asp 120 Asn Glu Lys Val Gly Glu Leu Gln Ala Lys Ala Leu Val Asp Ile Val 140 135 Pro Gln Gly Asn Tyr Phe Leu Met Gly Gly Ser Pro Val Asp Asn Asn 150 155 Ala Lys Leu Phe Arg Ala Gly Gln Met Lys Val Leu Lys Pro Tyr Val 170 Asp Ser Gly Lys Ile Lys Val Val Gly Asp Gln Trp Val Asp Gly Trp 185 Leu Pro Glu Asn Ala Leu Lys Ile Met Glu Asn Ala Leu Thr Ala Asn 205 200 Asn Asn Lys Ile Asp Ala Val Val Ala Ser Asn Asp Ala Thr Ala Gly 215 220 Gly Ala Ile Gln Ala Leu Ser Ala Gln Gly Leu Ser Gly Lys Val Ala 230 235 Ile Ser Gly Gln Asp Ala Asp Leu Ala Gly Ile Lys Arg Ile Ala Ala 250 245 Gly Thr Gln Thr Met Thr Val Tyr Lys Pro Ile Thr Leu Leu Ala Asn 265 Thr Ala Ala Glu Ile Ala Val Glu Leu Gly Asn Gly Gln Glu Pro Lys 280 Ala Asp Thr Thr Leu Asn Asn Gly Leu Lys Asp Val Pro Ser Arg Leu 295 300 Leu Thr Pro Ile Asp Val Asn Lys Asn Asn Ile Lys Asp Thr Val Ile 310 315 Lys Asp Gly Phe His Lys Glu Ser Glu Leu 325

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<210> 344
<211> 55
<212> PRT
<213> Escherichia coli
<400> 344
Met Asn Lys Phe Ile Lys Val Ala Leu Val Gly Ala Val Leu Ala Thr
Leu Thr Ala Cys Thr Gly His Ile Glu Asn Arg Asp Lys Asn Cys Ser
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                              25
Tyr Asp Tyr Leu Leu His Pro Ala Ile Ser Ile Ser Lys Ile Ile Gly
      35
                40
Gly Cys Gly Pro Thr Ala Gln
   50
<210> 345
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Leu Ala Ile Ala Val Gly Thr Thr Val Gly Ser Gly Ile Phe Val Ser
                           40
Val Gly Glu Val Ala Lys Ala Ala Gly Thr Pro Trp Leu Thr Val Leu
                      55
                                         60
Ala Phe Val Ile Gly Gly Leu Ile Val Ile Pro Gln Met Cys Val Tyr
                  70
                                     75
Ala Glu Leu Ser Thr Ala Tyr Pro Glu Asn Gly Ala Asp Tyr Val Tyr
              85
                                 90
Leu Lys Asn Ala Gly Ser Arg Pro Leu Ala Phe Leu Ser Gly Trp Ala
                                                 110
                              105
Ser Phe Trp Ala Asn Asp Ala Pro Ser Leu Ser Ile Met Ala Leu Ala
                          120
                                              125
Ile Val Ser Asn Leu Gly Phe Leu Thr Pro Ile Asp Pro Leu Leu Gly
                                          140
                       135
Lys Phe Ile Ala Ala Gly Leu Ile Ile Ala Phe Met Leu Leu His Leu
                   150
                                      155
Arg Ser Val Glu Gly Gly Ala Ala Phe Gln Thr Leu Ile Thr Ile Ala
                                  170
               165
Lys Ile Ile Pro Phe Thr Ile Val Ile Gly Leu Gly Ile Phe Trp Phe
                              185
           180
Lys Ala Glu Asn Phe Ala Ala Pro Thr Thr Thr Ala Ile Gly Ala Thr
                          200
                                              205
Gly Ser Phe Met Ala Leu Leu Ala Gly Ile Ser Ala Thr Ser Trp Ser
                                          220
                      215
Tyr Thr Gly Met Ala Ser Ile Cys Tyr Met Thr Gly Glu Ile Lys Asn
                  230
                                      235
Pro Gly Lys Thr Met Pro Arg Ala Leu Ile Gly Ser Cys Leu Leu Val
                                   250
             245
Leu Val Leu Tyr Thr Leu Leu Ala Leu Val Ile Ser Gly Leu Met Pro
                              265
                                                  270
Phe Asp Lys Leu Ala Asn Ser Glu Thr Pro Ile Ser Asp Ala Leu Thr
       275 280
Trp Ile Pro Ala Leu Gly Ser Thr Ala Gly Ile Phe Val Ala Ile Thr
                       295
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Ala Met Ile Val Ile Leu Gly Ser Leu Ser Ser Cys Val Met Tyr Gln
                   310
                                       315
Pro Arg Leu Glu Tyr Ala Met Ala Lys Asp Asn Leu Phe Phe Lys Cys
               325
                                   330
Phe Gly His Val His Pro Lys Tyr Asn Thr Pro Asp Val Ser Ile Ile
          340
                              345
                                                  350
Leu Gln Gly Ala Leu Gly Ile Phe Phe Ile Phe Val Ser Asp Leu Thr
                          360
Ser Leu Leu Gly Tyr Phe Thr Leu Val Met Cys Phe Lys Asn Thr Leu
                      375
Thr Phe Gly Ser Ile Ile Trp Cys Arg Lys Arg Asp Asp Tyr Lys Pro
               390
                                   395
Leu Trp Arg Thr Pro Ala Phe Gly Leu Met Thr Thr Leu Ala Ile Ala
             405
                                 410
Ser Ser Leu Ile Leu Val Ala Ser Thr Phe Val Trp Ala Pro Ile Pro
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                               425
Gly Leu Ile Cys Ala Val Ile Val Ile Ala Thr Gly Leu Pro Ala Tyr
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Ala Phe Trp Ala Lys Arg Ser Arg Gln Leu Asn Ala Leu Ser
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Ser His Asp Val Pro Leu Val His Ala Ile Val Glu Glu Met Val Lys
                          40
Arg Asp Ile Asp Arg Ile Tyr Phe Val Ala Cys Gly Ser Pro Leu Asn
                    55
Ala Ala Gln Thr Ala Lys His Leu Ala Asp Arg Phe Ser Asp Leu Gln
Val Tyr Ala Ile Ser Gly Trp Glu Phe Cys Asp Asn Thr Pro Tyr Arg
                                 90
Leu Asp Asp Arg Cys Ala Val Ile Gly Val Ser Asp Tyr Gly Lys Thr
          100
                             105
Glu Glu Val Ile Lys Ala Leu Glu Leu Gly Arg Ala Cys Gly Ala Leu
                          120
                                             125
Thr Ala Ala Phe Thr Lys Arg Ala Asp Ser Pro Ile Thr Ser Ala Ala
                      135
                                          140
Glu Phe Ser Ile Asp Tyr Gln Ala Asp Cys Ile Trp Glu Ile His Leu
                   150
                                     155 .
Leu Leu Cys Tyr Ser Val Val Leu Glu Met Ile Thr Arg Leu Ala Pro
                                  170
               165
Asn Ala Glu Ile Gly Lys Ile Lys Asn Asp Leu Lys Gln Leu Pro Asn
                              185
Ala Leu Gly His Leu Val Arg Thr Trp Glu Glu Lys Gly Arg Gln Leu
                         200
                                              205
Gly Glu Leu Ala Ser Gln Trp Pro Met Ile Tyr Thr Val Ala Ala Gly
                      215
                                          220
Pro Leu Arg Pro Leu Gly Tyr Lys Glu Gly Ile Val Thr Leu Met Glu
                                      235
                  230
Phe Thr Trp Thr His Gly Cys Val Ile Glu Ser Gly Glu Phe Arg His
              245
                                   250
Gly Pro Leu Glu Ile Val Glu Pro Gly Val Pro Phe Leu Phe Leu Leu
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265
Gly Asn Asp Glu Ser Arg His Thr Thr Glu Arg Ala Ile Asn Phe Val
                        280
Lys Gln Arg Thr Asp Asn Val Ile Val Ile Asp Tyr Ala Glu Ile Ser
                      295
Gln Gly Leu His Pro Trp Leu Ala Pro Phe Leu Met Phe Val Pro Met
                  310
                                   315
Glu Trp Leu Cys Tyr Tyr Leu Ser Ile Tyr Lys Asp His Asn Pro Asp
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Glu Arg Arg Tyr Tyr Gly Gly Leu Val Glu Tyr
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Met Asn Ala Ala Ile Thr Val Val Trp Trp Asn Ile Asn Pro Ser Pro
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Gly Pro Ala Thr Gly Arg Ile Tyr Ala Arg Ser Tyr Pro Met Lys Thr
Gly Met Phe Thr Cys Gly His Gln Arg Leu Pro Ile Glu His Ala Phe
                           40
Arg Asp Ala Ser Glu Leu Gly Tyr Asp Gly Ile Glu Ile Trp Gly Gly
                      55
Arg Pro His Ala Phe Ala Pro Asp Leu Lys Ala Gly Gly Ile Lys Gln
                   70
Ile Lys Ala Leu Ala Gln Thr Tyr Gln Met Pro Ile Ile Gly Tyr Thr
                                  90
Pro Glu Thr Asn Gly Tyr Pro Tyr Asn Met Met Leu Gly Asp Glu His
                              105
Met Arg Arg Glu Ser Leu Asp Met Ile Lys Leu Ala Met Asp Met Ala
                          120
Lys Glu Met Asn Ala Gly Tyr Thr Leu Ile Ser Ala Gly Pro Arg Gly
  130
                      135
Leu Ser His Ala Thr
145
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Met Arg Asp Ile Gln Met Val Leu Glu Arg Trp Gly Ala Trp Ala Ala
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Asn Asn His Glu Asp Val Thr Trp Ser Ser Ile Ala Ala Gly Phe Lys
                               25
Gly Leu Ile Thr Ser Lys Val Lys Ser Arg Pro Gln Cys Cys Asp Asp
                         40
Asp Ala Met Ile Ile Cys Gly Cys Met Ala Arg Leu Lys Lys Asn Asn
Ser Asp Leu His Asp Leu Leu Val Asp Tyr Tyr Val Val Gly Met Thr
                                      75
Phe Met Ser Leu Ala Gly Lys His Cys Cys Ser Asp Gly Tyr Ile Gly
                                  90
Lys Arg Leu Gln Lys Ala Glu Gly Ile Ile Glu Gly Met Leu Met Ala
           100 105
Leu Asp Ile Arg Leu Glu Met Asp Ile Val Val Asn Asn Ser Asn
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115 120 125

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<211> 453

<212> PRT

<213> Escherichia coli

<400> 349

Met Phe Asp Asn Leu Thr Asp Arg Leu Ser Arg Thr Leu Arg Asn Ile

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Ser Gly Arg Gly Arg Leu Thr Glu Asp Asn Val Lys Asp Thr Leu Arg
20 25 30

Clu Val Arg Met Ala Leu Leu Glu Ala Asp Val Ala Leu Bro Val Val

Glu Val Arg Met Ala Leu Leu Glu Ala Asp Val Ala Leu Pro Val Val 35 40 45

Arg Glu Phe Ile Asn Arg Val Lys Glu Lys Ala Val Gly His Glu Val 50 55 60

Asn Lys Ser Leu Thr Pro Gly Gln Glu Phe Val Lys Ile Val Arg Asn 65 70 75 80

Glu Leu Val Ala Ala Met Gly Glu Glu Asn Gln Thr Leu Asn Leu Ala 85 90 95

Ala Gln Pro Pro Ala Val Val Leu Met Ala Gly Leu Gln Gly Ala Gly 100 105 110

Lys Thr Thr Ser Val Gly Lys Leu Gly Lys Phe Leu Arg Glu Lys His 115 120 125

Lys Lys Lys Val Leu Val Val Ser Ala Asp Val Tyr Arg Pro Ala Ala 130 135 140

Ile Lys Gln Leu Glu Thr Leu Ala Glu Gln Val Gly Val Asp Phe Phe 145 150 155 160

Pro Ser Asp Val Gly Gln Lys Pro Val Asp Ile Val Asn Ala Ala Leu 165 170 175

Lys Glu Ala Lys Leu Lys Phe Tyr Asp Val Leu Leu Val Asp Thr Ala 180 185 190 Gly Arg Leu His Val Asp Glu Ala Met Met Asp Glu Ile Lys Gln Val

195 200 205
His Ala Ser Ile Asn Pro Val Glu Thr Leu Phe Val Val Asp Ala Met

210 215 220
Thr Gly Gln Asp Ala Ala Asn Thr Ala Lys Ala Phe Asn Glu Ala Leu
225 230 235 240

225 230 235 240 Pro Leu Thr Gly Val Val Leu Thr Lys Val Asp Gly Asp Ala Arg Gly

245 250 255

Gly Ala Ala Leu Ser Ile Arg His Ile Thr Gly Lys Pro Ile Lys Phe
260 265 270

Leu Gly Val Gly Glu Lys Thr Glu Ala Leu Glu Pro Phe His Pro Asp 275 280 285

Arg Ile Ala Ser Arg Ile Leu Gly Met Gly Asp Val Leu Ser Leu Ile
290 295 300

Glu Asp Ile Glu Ser Lys Val Asp Arg Ala Gln Ala Glu Lys Leu Ala

305 310 315 320 Ser Lys Leu Lys Lys Gly Asp Gly Phe Asp Leu Asn Asp Phe Leu Glu

325 330 335

Gln Leu Arg Gln Met Lys Asn Met Gly Gly Met Ala Ser Leu Met Gly
340 345 350

Lys Leu Pro Gly Met Gly Gln Ile Pro Asp Asn Val Lys Ser Gln Met

355 360 365
Asp Asp Lys Val Leu Val Arg Met Glu Ala Ile Ile Asn Ser Met Thr

370 375 380
Met Lys Glu Arg Ala Lys Pro Glu Ile Ile Lys Gly Ser Arg Lys Arg

Met Lys Glu Arg Ala Lys Pro Glu IIe IIe Lys Gly Ser Arg Lys Arg 385 390 395 400 Arg Ile Ala Ala Gly Cys Gly Met Gln Val Gln Asp Val Asn Arg Leu

11e Ala Ala Gly Cys Gly Met Gin Val Gin Asp Val Asn Arg
405 410 415

Leu Lys Gln Phe Asp Asp Met Gln Arg Met Met Lys Lys Met Lys Lys 425 Gly Gly Met Ala Lys Met Met Arg Ser Met Lys Gly Met Met Pro Pro 440 Gly Phe Pro Gly Arg 450 <210> 350 <211> 577 <212> PRT <213> Escherichia coli <400> 350 Met Lys Gln Gln Ile Gln Leu Arg Arg Arg Glu Val Asp Glu Thr Ala 10 Asp Leu Pro Ala Glu Leu Pro Pro Leu Leu Arg Arg Leu Tyr Ala Ser 20 25 Arg Gly Val Arg Ser Ala Gln Glu Leu Glu Arg Ser Val Lys Gly Met 40 Leu Pro Trp Gln Gln Leu Ser Gly Val Glu Lys Ala Val Glu Ile Leu 55 Tyr Asn Ala Phe Arg Glu Gly Thr Arg Ile Ile Val Val Gly Asp Phe 70 Asp Ala Asp Gly Ala Thr Ser Thr Ala Leu Ser Val Leu Ala Met Arg 90 Ser Leu Gly Cys Ser Asn Ile Asp Tyr Leu Val Pro Asn Arg Phe Glu 100 105 Asp Gly Tyr Gly Leu Ser Pro Glu Val Val Asp Gln Ala His Ala Arg 120 115 Gly Ala Gln Leu Ile Val Thr Val Asp Asn Gly Ile Ser Ser His Ala 135 Gly Val Glu His Ala Arg Ser Leu Gly Ile Pro Val Ile Val Thr Asp 150 155 His His Leu Pro Gly Asp Thr Leu Pro Ala Ala Glu Ala Ile Ile Asn 170 165 Pro Asn Leu Arg Asp Cys Asn Phe Pro Ser Lys Ser Leu Ala Gly Val 185 180 Gly Val Ala Phe Tyr Leu Met Leu Ala Leu Arg Thr Phe Leu Arg Asp Gln Gly Trp Phe Asp Glu Arg Asn Ile Ala Ile Pro Asn Leu Ala Glu 215 Leu Leu Asp Leu Val Ala Leu Gly Thr Val Ala Asp Val Val Pro Leu 230 235 Asp Ala Asn Asn Arg Ile Leu Thr Trp Gln Gly Met Ser Arg Ile Arg 250 Ala Gly Lys Cys Arg Pro Gly Ile Lys Ala Leu Leu Glu Val Ala Asn 265 Arg Asp Ala Gln Lys Leu Ala Ala Ser Asp Leu Gly Phe Ala Leu Gly 280 Pro Arg Leu Asn Ala Ala Gly Arg Leu Asp Asp Met Ser Val Gly Val 300 295 Ala Leu Leu Cys Asp Asn Ile Gly Glu Ala Arg Val Leu Ala Asn 310 315 Glu Leu Asp Ala Leu Asn Gln Thr Arg Lys Glu Ile Glu Gln Gly Met 325 330 Gln Ile Glu Ala Leu Thr Leu Cys Glu Lys Leu Glu Arg Ser Arg Asp 345 350 Thr Leu Pro Gly Gly Leu Ala Met Tyr His Pro Glu Trp His Gln Gly 360 365 Val Val Gly Ile Leu Ala Ser Arg Ile Lys Glu Arg Phe His Arg Pro

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375
                                         380
Val Ile Ala Phe Ala Pro Ala Gly Asp Gly Thr Leu Lys Gly Ser Gly
                  390
                                     395
Arg Ser Ile Gln Gly Leu His Met Arg Asp Ala Leu Glu Arg Leu Asp
              405
                                  410
Thr Leu Tyr Pro Gly Met Met Leu Lys Phe Gly Gly His Ala Met Ala
                             425
          420
Ala Gly Leu Ser Leu Glu Glu Asp Lys Phe Lys Leu Phe Gln Gln Arg
                         440
       435
Phe Gly Glu Leu Val Thr Glu Trp Leu Asp Pro Ser Leu Leu Gln Gly
                     455
Glu Val Val Ser Asp Gly Pro Leu Ser Pro Ala Glu Met Thr Met Glu
                           475
          470
Val Ala Gln Leu Leu Arg Asp Ala Gly Pro Trp Gly Gln Met Phe Pro
            485
                                 490
Glu Pro Leu Phe Asp Gly His Phe Arg Leu Leu Gln Gln Arg Leu Val
                              505
Gly Glu Arg His Leu Lys Val Met Val Glu Pro Val Gly Gly Gly Pro
                          520
                                             525
Leu Leu Asp Gly Ile Ala Phe Asn Val Asp Thr Ala Leu Trp Pro Asp
                      535
                                         540
Asn Gly Val Arg Glu Val Gln Leu Ala Tyr Lys Leu Asp Ile Asn Glu
                   550
                                    555
Phe Arg Gly Asn Arg Ser Leu Gln Ile Ile Ile Asp Asn Ile Trp Pro
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                                 570
Ile
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Phe Ala Gln Ala Asp Asp Ala Ala Ile Gln Gln Thr Leu Ala Lys Met
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Gly Ile Lys Ser Ser Asp Ile Gln Pro Ala Pro Val Ala Gly Met Lys
                         40
Thr Val Leu Thr Asn Ser Gly Val Leu Tyr Ile Thr Asp Asp Gly Lys
                                        60
              55
His Ile Ile Gln Gly Pro Met Tyr Asp Val Ser Gly Thr Ala Pro Val
                                     75
                  70
Asn Val Thr Asn Lys Met Leu Leu Lys Gln Leu Asn Ala Leu Glu Lys
                                  90
Glu Met Ile Val Tyr Lys Ala Pro Gln Glu Lys His Val Ile Thr Val
           100
                              105
Phe Thr Asp Ile Thr Cys Gly Tyr Cys His Lys Leu His Glu Gln Met
                          120
                                            125
      115
Ala Asp Tyr Asn Ala Leu Gly Ile Thr Val Arg Tyr Leu Ala Phe Pro
                      135
                                         140
Arg Gln Gly Leu Asp Ser Asp Ala Glu Lys Glu Met Lys Ala Ile Trp
                  150
                                    155
Cys Ala Lys Asp Lys Asn Lys Ala Phe Asp Asp Val Met Ala Gly Lys
                                 170
              165
                                                    175
Ser Val Ala Pro Ala Ser Cys Asp Val Asp Ile Ala Asp His Tyr Ala
          180
                             185
Leu Gly Val Gln Leu Gly Val Ser Gly Thr Pro Ala Val Val Leu Ser
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Asn Gly Thr Leu Val Pro Gly Tyr Gln Pro Pro Lys Glu Met Lys Glu
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Phe Leu Asp Glu His Gln Lys Met Thr Ser Gly Lys
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<211> 298
<212> PRT
<213> Escherichia coli
<400> 352
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Leu Glu Lys Asn Leu Ala Glu Asn Thr Leu Asn Ala Tyr Arg Arg Asp
                             25
Leu Ser Met Met Val Glu Trp Leu His His Arg Gly Leu Thr Leu Ala
                         40
Thr Ala Gln Ser Asp Asp Leu Gln Ala Leu Leu Ala Glu Arg Leu Glu
                          • • 60
                     55
Gly Gly Tyr Lys Ala Thr Ser Ser Ala Arg Leu Leu Ser Ala Val Arg
                                   75
Arg Leu Phe Gln Tyr Leu Tyr Arg Glu Lys Phe Arg Glu Asp Asp Pro
                               90
             85
Ser Ala His Leu Ala Ser Pro Lys Leu Pro Gln Arg Leu Pro Lys Asp
                           105
          100
Leu Ser Glu Ala Gln Val Glu Arg Leu Leu Gln Ala Pro Leu Ile Asp
                        120
                                            125
Gln Pro Leu Glu Leu Arg Asp Lys Ala Met Leu Glu Val Leu Tyr Ala
                                       140
                     135
Thr Gly Leu Arg Val Ser Glu Leu Val Gly Leu Thr Met Ser Asp Ile
                  150
                                    155
Ser Leu Arg Gln Gly Val Val Arg Val Ile Gly Lys Gly Asn Lys Glu
                   170
             165
Arg Leu Val Pro Leu Gly Glu Glu Ala Val Tyr Trp Leu Glu Thr Tyr
                            185
          180
Leu Glu His Gly Arg Pro Trp Leu Leu Asn Gly Val Ser Ile Asp Val
                        200
Leu Phe Pro Ser Gln Arg Ala Gln Gln Met Thr Arg Gln Thr Phe Trp
                             220
          215
His Arg Ile Lys His Tyr Ala Val Leu Ala Gly Ile Asp Ser Glu Lys
        230 235
Leu Ser Pro His Val Leu Arg His Ala Phe Ala Thr His Leu Leu Asn
                                 250
His Gly Ala Asp Leu Arg Val Val Gln Met Leu Leu Gly His Ser Asp
                             265
Leu Ser Thr Thr Gln Ile Tyr Thr His Val Ala Thr Glu Arg Leu Arg
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Gln Leu His Gln Gln His His Pro Arg Ala
<210> 353
<211> 246
<212> PRT
<213> Escherichia coli
<400> 353
Met Phe Phe Asn Thr Lys His Thr Thr Ala Leu Cys Phe Val Thr Cys
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Met Ala Phe Ser Ser Ser Ile Ala Asp Ile Val Ile Ser Gly Thr
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Arg Val Ile Tyr Lys Ser Asp Gln Lys Ser Val Asn Val Arg Leu Glu
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Asn Lys Gly Asn Asn Pro Leu Leu Val Gln Ser Trp Leu Asp Thr Gly
Asp Asp Asn Ala Glu Pro Gly Ser Ile Thr Val Pro Phe Thr Ala Thr
Pro Pro Val Ser Arg Ile Asp Ala Lys Arg Gly Gln Thr Ile Lys Leu
Met Tyr Thr Ala Ser Thr Ser Leu Pro Lys Asp Arg Glu Ser Val Phe
                             105
Trp Phe Asn Val Leu Glu Val Pro Pro Lys Pro Asp Ala Glu Lys Val
                          120
Ala Asn Gln Ser Leu Leu Gln Leu Ala Phe Arg Thr Arg Ile Lys Leu
                                         140
           135
Phe Tyr Arg Pro Asp Gly Leu Lys Gly Asn Pro Ser Glu Ala Pro Leu
                  150
                              155
Ala Leu Lys Trp Phe Trp Ser Gly Ser Glu Gly Lys Ala Ser Leu Arg
            165
                                  170
Val Thr Asn Pro Thr Pro Tyr Tyr Val Ser Phe Ser Ser Gly Asp Leu
                              185
                                                190
Glu Ala Ser Gly Lys Arg Tyr Pro Ile Asp Val Lys Met Ile Ala Pro
                         200
Phe Ser Asp Glu Val Met Lys Val Asn Gly Leu Asn Gly Lys Ala Asn
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Ser Ala Lys Val His Phe Tyr Ala Ile Asn Asp Phe Gly Gly Ala Ile
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Glu Gly Asn Ala Arg Leu
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<212> PRT

<213> Escherichia coli

<400> 354

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		195					200					205			
	210					215					220		Met		
225	_				230					235			Arg		240
				245					250				Thr	255	
			260					265					Tyr 270		
	_	275					280					285	Ile		
_	290					295					300		Gly		
305		_			310					315			Ile		320
				325					330				Ile	335	
	=	_	340					345					Ser 350		
		355					360					365	Gly		
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385		_			390					395			Gly		400
				405					410				Gly	415	
			420					425					Asn 430		
		435					440					445	Val		
	450					455					460		Ala		
465	-				470					475			Leu		480
	•			485					490				Lys	495	
			500					505					Ile 510		
		515					520					525	Leu		
	530					535					540		Asn		
545					550					555			Val		560
			_	565					570					575	Leu
			580					585					5 <del>9</del> 0		Thr
	_	595					600					605			Gly
	610					615					620				Arg
625		_			630					635			.*		Lys 640
_				645					650					655	
			660					665					670		Val
Ser	Leu	Ser	Thr	Asp	Gly	Gly	Phe	Val	Leu	His	Ser	Gly	Gly	Leu	Thr

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680
       675
Phe Ser Asn Asp Ser Phe Ser Asp Ser Asp Thr Leu Ala Val Val Gln
                      695
Ala Pro Gly Ala Gln Gly Ala Arg Ile Asn Tyr Gly Asn Ser Thr Ile
                  710
                                     715
Asp Arg Trp Gly Tyr Gly Val Thr Ser Ala Leu Ser Pro Tyr His Glu
               725
                        730
Asn Arg Ile Ala Leu Asp Ile Asn Asp Leu Glu Asn Asp Val Glu Leu
                             745
Lys Ser Thr Ser Ala Val Ala Val Pro Arg Gln Gly Ser Val Val Phe
                760
Ala Asp Phe Glu Thr Val Gln Gly Gln Ser Ala Ile Met Asn Ile Thr
                   775
                                         780
Arg Ser Asp Gly Lys Asn Ile Pro Phe Ala Ala Asp Ile Tyr Asp Glu
                   790
                                      795
Gln Gly Asn Val Ile Gly Asn Val Gly Gln Gly Gln Ala Phe Val
                                  810
Arg Gly Ile Glu Gln Gln Gly Asn Ile Ser Ile Lys Trp Leu Glu Gln
                              825
           820
Ser Lys Pro Val Ser Cys Leu Ala His Tyr Gln Gln Ser Pro Glu Ala
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Glu Lys Ile Ala Gln Ser Ile Ile Leu Asn Gly Ile Arg Cys Gln Ile
Gln
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His Asn Pro Tyr Trp Arg Leu Thr Glu Ser Ser Asp Val Leu Arg Phe
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Ser Thr Thr Glu Thr Thr Glu Pro Asp Arg Thr Leu Gln Leu Ser Ala
                          40
Glu Gln Ala Ala Arg Ile Arg Glu Met Thr Val Ile Thr Ser Ser Leu
                      55
                                         60
Met Met Ser Leu Thr Val Asp Glu Ser Asp Leu Ser Val His Leu Val
        70
                                     75
Gly Arg Lys Ile Asn Lys Arg Glu Trp Ala Gly Asn Ala Ser Ala Trp
                                  90
His Asp Thr Pro Ala Val Ala Arg Asp Leu Ser His Gly Leu Ser Phe
           100
                              105
Ala Glu Gln Val Val Ser Glu Ala His Ser Ala Ile Val Ile Leu Asp
                          120
Ser Arg Gly Asn Ile Gln Arg Phe Asn Arg Leu Cys Glu Asp Tyr Thr
                      135
                                          140
Gly Leu Lys Glu His Asp Val Ile Gly Gln Ser Val Phe Lys Leu Phe
                   150
                                     155
Met Ser Arg Arg Glu Ala Ala Ala Ser Arg Arg Asn Asn Arg Val Phe
              165
                                 170
Phe Arg Ser Gly Asn Ala Tyr Glu Val Glu Leu Trp Ile Pro Thr Cys
                             185
                                                190
           180
Lys Gly Gln Arg Leu Phe Leu Phe Arg Asn Lys Phe Val His Ser Gly
                         200
                                             205
Ser Gly Lys Asn Glu Ile Phe Leu Ile Cys Ser Gly Thr Asp Ile Thr
                       215
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PCT/US00/30950 WO 01/34810

Glu 225	Glu	Arg	Arg	Ala	Gln 230	Glu	Arg	Leu	Arg	Ile 235	Leu	Ala	Asn	Thr	Asp 240
Ser	Ile	Thr	Gly	Leu 245	Pro	Asn	Arg	Asn	Ala 250	Met	Gln	Asp	Leu	Ile 255	Asp
His	Ala	Ile	Asn 260	His	Ala	Asp	Asn	Asn 265	Lys	Val	Gly	Val	Val 270	Tyr	Leu
Asp	Leu	Asp 275	Asn	Phe	Lys	Lys	Val 280	Asn	Asp	Ala	Tyr	Gly 285	His	Leu	Phe
_	290				Arg	295					300			•	
305		_			Leu 310					315					320
				325	Ser				330					335	
			340		Arg			345					350		
_		355	-		Val		360					365			
_	370				Ile	375					380				
385		_			Gly 390			:		395					400
	-			405	Tyr				410					415	
•			420		Leu			425					430		
_	_	435		_	Ser		440					445			
	450	_				455					460				
465	_				Pro 470					475					480
				485	Trp				490					495	
			500		Arg			505	_				510		
	_	515			Gln		520					525			
	530				Ser	535					540				
545					Phe 550					555					560
_				565	Tyr				570					575	
	-		580					585					590		Lys
		595					600					605			Gln
	610				Val	615					620				
625					Lys 630					635					640
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<210> 356 <211> 230 <212> PRT

## <213> Escherichia coli

Met Met Thr Lys Ile Lys Leu Leu Met Leu Ile Ile Phe Tyr Leu Ile Ile Ser Ala Ser Ala His Ala Ala Gly Gly Ile Ala Leu Gly Ala Thr 25 Arg Ile Ile Tyr Pro Ala Asp Ala Lys Gln Thr Ala Val Trp Ile Arg Asn Ser His Thr Asn Glu Arg Phe Leu Val Asn Ser Trp Ile Glu Asn 55 Ser Ser Gly Val Lys Glu Lys Ser Phe Ile Ile Thr Pro Pro Leu Phe 75 70 Val Ser Glu Pro Lys Ser Glu Asn Thr Leu Arg Ile Ile Tyr Thr Gly 85 90 Pro Pro Leu Ala Ala Asp Arg Glu Ser Leu Phe Trp Met Asn Val Lys 105 Thr Ile Pro Ser Val Asp Lys Asn Ala Leu Asn Gly Arg Asn Val Leu 120 125 Gln Leu Ala Ile Leu Ser Arg Met Lys Leu Phe Leu Arg Pro Ile Gln 135 140 Leu Gln Glu Leu Pro Ala Glu Ala Pro Asp Thr Leu Lys Phe Ser Arg 150 155 Ser Gly Asn Tyr Ile Asn Val His Asn Pro Ser Pro Phe Tyr Val Thr 165 170 Leu Val Asn Leu Gln Val Gly Ser Gln Lys Leu Gly Asn Ala Met Ala 185 180 Ala Pro Arg Val Asn Ser Gln Ile Pro Leu Pro Ser Gly Val Gln Gly 195 200 Lys Leu Lys Phe Gln Thr Val Asn Asp Tyr Gly Ser Val Thr Pro Val Arg Glu Val Asn Leu Asn 225 <210> 357 <211> 867 <212> PRT <213> Escherichia coli <400> 357 Met Lys Ile Pro Thr Thr Thr Asp Ile Pro Gln Arg Tyr Thr Trp Cys 10 Leu Ala Gly Ile Cys Tyr Ser Ser Leu Ala Ile Leu Pro Ser Phe Leu 25 Ser Tyr Ala Glu Ser Tyr Phe Asn Pro Ala Phe Leu Leu Glu Asn Gly Thr Ser Val Ala Asp Leu Ser Arg Phe Glu Arg Gly Asn His Gln Pro 60 55 Ala Gly Val Tyr Arg Val Asp Leu Trp Arg Asn Asp Glu Phe Ile Gly 70 75 Ser Gln Asp Ile Val Phe Glu Ser Thr Thr Glu Asn Thr Gly Asp Lys Ser Gly Gly Leu Met Pro Cys Phe Asn Gln Val Leu Leu Glu Arg Ile 105 Gly Leu Asn Ser Ser Ala Phe Pro Glu Leu Ala Gln Gln Asn Asn 120 125 Lys Cys Ile Asn Leu Leu Lys Ala Val Pro Asp Ala Thr Ile Asn Phe 135 140 Asp Phe Ala Ala Met Arg Leu Asn Ile Thr Ile Pro Gln Ile Ala Leu 150 155

														_	
Leu	Ser	Ser	Ala	His 165	Gly	Tyr	Ile	Pro	Pro 170	Glu	Glu	Trp	Asp	Glu 175	Gly
Ile	Pro	Ala	Leu 180	Leu	Leu	Asn	Tyr	Asn 185	Phe	Thr	Gly	Asn	Arg 190	Gly	Asn
Gly	Asn	Asp 195		Tyr	Phe	Phe	Ser 200		Leu	Ser	Gly	Ile 205		Ile	Gly
Pro	Trp 210	Arg	Leu	Arg	Asn	Asn 215	Gly	Ser	Trp	Asn	Tyr 220	Phe	Arg	Gly	Asn
Gly 225	Tyr	His	Ser	Glu	Gln 230	Trp	Asn	Asn	Ile	Gly 235	Thr	Trp	Val	Gln	Arg 240
Ala	Ile	Ile	Pro	Leu 245	Lys	Ser	Glu	Leu	Val 250	Met	Gly	Asp	Gly	Asn 255	Thr
Gly	Ser	Asp	Ile 260	Phe	Asp	Gly	Val	Gly 265	Phe	Arg	Gly	Val	Arg 270	Leu	Tyr
Ser	Ser	Asp 275	Asn	Met	Tyr	Pro	Asp 280	Ser	Gln	Gln	Gly	Phe 285	Ala	Pro	Thr
Val	Arg 290	Gly	Ile	Alá	Arg	Thr 295	Ala	Ala	Gln	Leu	Thr 300	Ile	Arg	Gln	Asn
Gly 305	Phe	Ile	Ile	Tyr	Gln 310	Ser	Tyr	Val	Ser	Pro 315	Gly	Ala	Phe	Glu	Ile 320
Thr	Asp	Leu	His	Pro 325	Thr	Ser	Ser	Asn	Gly 330	Asp	Leu	Asp	Val	Thr 335	Ile
Asp	Glu	Arg	Asp 340	Gly	Asn	Gln	Gln	Asn 345	Tyr	Thr	Ile	Pro	Tyr 350		Thr
		355			Arg		360					365			
Gly	Asp 370	Phe	Arg	Ser	Gly	Asn 375	Ser	Gln	Gln	Ser	Ser 380	Pro	Phe	Phe	Phe
Gln 385	Gly	Thr	Ala	Leu	Gly 390	Gly	Leu	Pro	Gln	Glu 395	Phe	Thr	Ala	Tyr	Gly 400
_				405	Ala				410					415	
_			420		Trp			425					430		
		435			Asp		440					445			
	450	_		-	Ser	455					460				
465					Ser 470					475					480
Ala	Tyr	Arg	Arg	Met 485	Glu	Gly	Tyr	Glu	Tyr 490	Asp	Tyr	Asp	Gly	Glu 495	His
	-		500		Ile			505					510		
-	_	515					520					525			Gly
	530	-			Gly	535			_		540				
545	_		_	_	Gln 550		_			555					560
				565	Phe				570					575	
Asn	Glu	Arg	Ile 580	Val	Gly	Leu	Asn	Val 585	Ser	Val	Pro	Phe	Asn 590	Val	Leu
	_	595	_				600					605			Ala
Ser	Phe 610	Asn	Ala	Asn	Arg	Asn 615	Ser	Asn	Gly	Gln	Asn 620	Ser	Trp	Leu	Ala
Gly 625	Val	Gly	Gly	Thr	Leu 630	Leu	Glu	Gly	His	Asn 635	Leu	Ser	Tyr	His	Val 640

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Ser Gln Gly Asp Thr Ser Asn Asn Gly Tyr Thr Gly Ser Ala Thr Ala
             645
                              650
Asn Trp Gln Ala Ala Tyr Gly Thr Leu Gly Gly Gly Tyr Asn Tyr Asp
                           665
Arg Asp Gln His Asp Val Asn Trp Gln Leu Ser Gly Gly Val Val Gly
              680
His Glu Asn Gly Ile Thr Leu Ser Gln Pro Leu Gly Asp Thr Asn Val
        695
                            700
Leu Ile Lys Ala Pro Gly Ala Gly Gly Val Arg Ile Glu Asn Gln Thr
    710 715 720
Gly Ile Leu Thr Asp Trp Arg Gly Tyr Ala Val Met Leu Tyr Ala Thr
            725 730 735
Val Tyr Arg Tyr Asn Arg Ile Ala Leu Asp Thr Asn Thr Met Gly Asn
       740 745
Ser Ile Asp Val Glu Lys Asn Ile Ser Ser Val Val Pro Thr Gln Gly
   755 760
Ala Leu Val Arg Ala Asn Phe Asp Thr Arg Ile Gly Val Arg Ala Leu
                                     780
 770 775
Ile Thr Val Thr Gln Gly Gly Lys Pro Val Pro Phe Gly Ser Leu Val
                       795
                 790
Arg Glu Asn Ser Thr Gly Ile Thr Ser Met Val Gly Asp Asp Gly Gln
                              810
           805
Val Tyr Leu Ser Gly Ala Pro Leu Ser Gly Glu Leu Leu Val Gln Trp
                           825
Gly Asp Gly Ala Asn Ser Arg Cys Ile Ala His Tyr Val Leu Pro Lys
                                        845
                       840
Gln Ser Leu Gln Gln Ala Val Thr Val Ile Ser Ala Val Cys Thr His
  850
                   855
Pro Gly Ser
865
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<213> Escherichia coli
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Asn Ser Thr Gly Val Ala Glu Asp Glu His Tyr Asp Leu Ser Asn Ile
                           25
Phe Asn Ser Thr Asn Asn Gln Pro Gly Gln Ile Val Val Leu Pro Glu
 35 40
Lys Ser Gly Trp Val Gly Val Ser Ala Ile Cys Pro Pro Gly Thr Leu
Val Asn Tyr Thr Tyr Arg Ser Tyr Val Thr Asn Phe Ile Val Gln Glu
               70
                                 75
Thr Ile Asp Asn Tyr Lys Tyr Met Gln Leu His Asp Tyr Leu Leu Gly
            85
                             90
Ala Met Ser Leu Val Asp Ser Val Met Asp Ile Gln Phe Pro Pro Gln
                           105
Asn Tyr Ile Arg Met Gly Thr Asp Pro Asn Val Ser Gln Asn Leu Pro
                       120
Phe Gly Val Met Asp Ser Arg Leu Ile Phe Arg Leu Lys Val Ile Arg
                    135
                                     140
Pro Phe Ile Asn Met Val Glu Ile Pro Arg Gln Val Met Phe Thr Val
                150 155
Tyr Val Thr Ser Thr Pro Tyr Asp Pro Leu Val Thr Pro Val Tyr Thr
             165 170
                                                175
Ile Ser Phe Gly Gly Arg Val Glu Val Pro Gln Asn Cys Glu Leu Asn
```

```
185
         180
Ala Gly Gln Ile Val Glu Phe Asp Phe Gly Asp Ile Gly Ala Ser Leu
              200
Phe Ser Ala Ala Gly Pro Gly Asn Arg Pro Ala Gly Val Met Pro Gln
                    215
                             220
Thr Lys Ser Ile Ala Val Lys Cys Thr Asn Val Ala Ala Gln Ala Tyr
                        235
225 230
Leu Thr Met Arg Leu Glu Ala Ser Ala Val Ser Gly Gln Ala Met Val
    . 245 250
Ser Asp Asn Gln Asp Leu Gly Phe Ile Val Ala Asp Gln Asn Asp Thr
                265
Pro Ile Thr Pro Asn Asp Leu Asn Ser Val Ile Pro Phe Arg Leu Asp
                        280
                                         285
Ala Ala Ala Ala Asn Val Thr Leu Arg Ala Trp Pro Ile Ser Ile
                           300
                    295
Thr Gly Gln Lys Pro Thr Glu Gly Pro Phe Ser Ala Leu Gly Tyr Leu
305 310
Arg Val Asp Tyr Gln
             325
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<211> 171
<212> PRT
<213> Escherichia coli
<400> 359
Met Arg Arg Val Leu Phe Ser Cys Phe Cys Gly Leu Leu Trp Ser Ser
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Ser Gly Trp Ala Val Asp Pro Leu Gly Thr Ile Asn Ile Asn Leu His
                           25
          20
Gly Asn Val Val Asp Phe Ser Cys Thr Val Asn Thr Ala Asp Ile Asp
                       40
Lys Thr Val Asp Leu Gly Arg Trp Pro Thr Thr Gln Leu Leu Asn Ala
                    55
Gly Asp Thr Thr Ala Leu Val Pro Phe Ser Leu Arg Leu Glu Gly Cys
                         75
                70
Pro Pro Gly Ser Val Ala Ile Leu Phe Thr Gly Thr Pro Ala Ser Asp
                     90 95
             85
Thr Asn Leu Leu Ala Leu Asp Asp Pro Ala Met Ala Gln Thr Val Ala
                           105 110
         100
Ile Glu Leu Arg Asn Ser Asp Arg Ser Arg Leu Ala Leu Gly Glu Ala
                       120
                                          125
Ser Pro Thr Glu Glu Val Asp Ala Asn Gly Asn Val Thr Leu Asn Phe
                          140
                     135
Phe Ala Asn Tyr Arg Ala Leu Ala Ser Gly Val Arg Pro Gly Val Ala
                 150
                                   155
Lys Ala Asp Ala Ile Phe Met Ile Asn Tyr Asn
              165
<210> 360
<211> 194
<212> PRT
<213> Escherichia coli
<400> 360
Met Phe Gly Tyr Arg Ser Asn Val Pro Lys Val Arg Leu Thr Thr Asp
                               10
Arg Leu Val Val Arg Leu Val His Asp Arg Asp Ala Trp Arg Leu Ala
                           25
                                            30
          20
Asp Tyr Tyr Ala Glu Asn Arg His Phe Leu Lys Pro Trp Glu Pro Val
```

```
40
Arg Asp Glu Ser His Cys Tyr Pro Ser Gly Trp Gln Ala Arg Leu Gly
Met Ile Asn Glu Phe His Lys Gln Gly Ser Ala Phe Tyr Phe Gly Leu
                  70
Phe Asp Pro Asp Glu Lys Glu Ile Ile Gly Val Ala Asn Phe Ser Asn
              85
Val Val Arg Gly Ser Phe His Ala Cys Tyr Leu Gly Tyr Ser Ile Gly
                            105
          100
Gln Lys Trp Gln Gly Lys Gly Leu Met Phe Glu Ala Leu Thr Ala Ala
                        120
Ile Arg Tyr Met Gln Arg Thr Gln His Ile His Arg Ile Met Ala Asn
             135
                               140
Tyr Met Pro His Asn Lys Arg Ser Gly Asp Leu Leu Ala Arg Leu Gly
                          155
        150
Phe Glu Lys Glu Gly Tyr Ala Lys Asp Tyr Leu Leu Ile Asp Gly Gln
           165
                      170
                                                   175
Trp Arg Asp His Val Leu Thr Ala Leu Thr Thr Pro Asp Trp Thr Pro
          180
                            185
Gly Arg
<210> 361
<211> 215
<212> PRT
<213> Escherichia coli
<400> 361
Met Lys Tyr Gln Leu Thr Ala Leu Glu Ala Arg Val Ile Gly Cys Leu
Leu Glu Lys Gln Val Thr Thr Pro Glu Gln Tyr Pro Leu Ser Val Asn
                             25
Gly Val Val Thr Ala Cys Asn Gln Lys Thr Asn Arg Glu Pro Val Met
                         40
Asn Leu Ser Glu Ser Glu Val Gln Glu Gln Leu Asp Asn Leu Val Lys
                     55
Arg His Tyr Leu Arg Thr Val Ser Gly Phe Gly Asn Arg Val Thr Lys
Tyr Glu Gln Arg Phe Cys Asn Ser Glu Phe Gly Asp Leu Lys Leu Ser
              85
                                 90
Ala Ala Glu Val Ala Leu Ile Thr Thr Leu Leu Leu Arg Gly Ala Gln
        100 105
                                               110
Thr Pro Gly Glu Leu Arg Ser Arg Ala Ala Arg Met Tyr Glu Phe Ser
                         120
                                            125
Asp Met Ala Glu Val Glu Ser Thr Leu Glu Gln Leu Ala Asn Arg Glu
                      135
                                        140
Asp Gly Pro Phe Val Val Arg Leu Ala Arg Glu Pro Gly Lys Arg Glu
                                     155
                  150
Asn Arg Tyr Met His Leu Phe Ser Gly Glu Val Glu Asp Gln Pro Ala
                                 170
              165
Val Thr Asp Met Ser Asn Ala Val Asp Gly Asp Leu Gln Ala Arg Val
                             185
Glu Ala Leu Glu Ile Glu Val Ala Glu Leu Lys Gln Arg Leu Asp Ser
                 200
Leu Leu Ala His Leu Gly Asp
  210
<210> 362
<211> 307
<212> PRT
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-334-

Met Lys Lys Leu Arg Ile Gly Val Val Gly Leu Gly Gly Ile Ala Gln

## <213> Escherichia coli

<400> 362

10 Lys Ala Trp Leu Pro Val Leu Ala Ala Ala Ser Asp Trp Thr Leu Gln 20 25 Gly Ala Trp Ser Pro Thr Arg Ala Lys Ala Leu Pro Ile Cys Glu Ser 40 Trp Arg Ile Pro Tyr Ala Asp Ser Leu Ser Ser Leu Ala Ala Ser Cys 55 60 Asp Ala Val Phe Val His Ser Ser Thr Ala Ser His Phe Asp Val Val 70 75 Ser Thr Leu Leu Asn Ala Gly Val His Val Cys Val Asp Lys Pro Leu 90 85 Ala Glu Asn Leu Arg Asp Ala Glu Arg Leu Val Glu Leu Ala Ala Arg 105 Lys Lys Leu Thr Leu Met Val Gly Phe Asn Arg Arg Phe Ala Pro Leu 120 125 Tyr Gly Glu Leu Lys Thr Gln Leu Ala Thr Ala Ala Ser Leu Arg Met 135 140 Asp Lys His Arg Ser Asn Ser Val Gly Pro His Asp Leu Tyr Phe Thr 150 155 Leu Leu Asp Asp Tyr Leu His Val Val Asp Thr Ala Leu Trp Leu Ser 170 165 Gly Gly Lys Ala Ser Leu Asp Gly Gly Thr Leu Leu Thr Asn Asp Ala 180 185 Gly Glu Met Leu Phe Ala Glu His His Phe Ser Ala Gly Pro Leu Gln 200 Ile Thr Thr Cys Met His Arg Arg Ala Gly Ser Gln Arg Glu Thr Val 215 Gln Ala Val Thr Asp Gly Ala Leu Ile Asp Ile Thr Asp Met Arg Glu 230 235 Trp Arg Glu Glu Arg Gly Gln Gly Val Val His Lys Pro Ile Pro Gly 245 250 Trp Gln Ser Thr Leu Glu Gln Arg Gly Phe Val Gly Cys Ala Arg His 265 Phe Ile Glu Cys Val Gln Asn Gln Thr Val Pro Gln Thr Ala Gly Glu Gin Ala Val Leu Ala Gin Arg Ile Val Asp Lys Ile Trp Arg Asp Ala 295 300 Met Ser Glu 305 <210> 363 <211> 239 <212> PRT <213> Escherichia coli <400> 363 Met Leu Lys Arg Val Phe Leu Ser Leu Leu Val Leu Ile Gly Leu Leu 10 Leu Leu Thr Val Leu Gly Leu Asp Arg Trp Met Ser Trp Lys Thr Ala 20 25 Pro Tyr Ile Tyr Asp Glu Leu Gln Asp Leu Pro Tyr Arg Gln Val Gly Val Val Leu Gly Thr Ala Lys Tyr Tyr Arg Thr Gly Val Ile Asn Gln Tyr Tyr Arg Tyr Arg Ile Gln Gly Ala Ile Asn Ala Tyr Asn Ser Gly 75

```
Lys Val Asn Tyr Leu Leu Leu Ser Gly Asp Asn Ala Leu Gln Ser Tyr
                                   90
               85
Asn Glu Pro Met Thr Met Arg Lys Asp Leu Ile Ala Ala Gly Val Asp
                              105
            100
Pro Ser Asp Ile Val Leu Asp Tyr Ala Gly Phe Arg Thr Leu Asp Ser
                           120
Ile Val Arg Thr Arg Lys Val Phe Asp Thr Asn Asp Phe Ile Ile Ile
                      135
Thr Gln Arg Phe His Cys Glu Arg Ala Leu Phe Ile Ala Leu His Met
               150
                                155
Gly Ile Gln Ala Gln Cys Tyr Ala Val Pro Ser Pro Lys Asp Met Leu
                                  170
               165
Ser Val Arg Ile Arg Glu Phe Ala Ala Arg Phe Gly Ala Leu Ala Asp
                               185
Leu Tyr Ile Phe Lys Arg Glu Pro Arg Phe Leu Gly Pro Leu Val Pro
                           200
Ile Pro Ala Met His Gln Val Pro Glu Asp Ala Gln Gly Tyr Pro Ala
                       215
                                           220
Val Thr Pro Glu Gln Leu Leu Glu Leu Gln Lys Lys Gln Gly Lys
                   230
<210> 364
<211> 79
<212> PRT
<213> Escherichia coli
<400> 364
Met Asp Val Gln Gln Phe Phe Val Val Ala Val Phe Phe Leu Ile Pro
Ile Phe Cys Phe Arg Glu Ala Trp Lys Gly Trp Arg Ala Gly Ala Ile
Asp Lys Arg Val Lys Asn Ala Pro Glu Pro Val Tyr Val Trp Arg Ala
                           40
Lys Asn Pro Gly Leu Phe Phe Ala Tyr Met Val Ala Tyr Ile Gly Phe
                       55
Gly Ile Leu Ser Ile Gly Met Ile Val Tyr Leu Ile Phe Tyr Arg
                    70
<210> 365
<211> 510
<212> PRT
<213> Escherichia coli
<400> 365
Met Ala Thr Ile Asp Ser Met Asn Lys Asp Thr Thr Arg Leu Ser Asp
Gly Pro Asp Trp Thr Phe Asp Leu Leu Asp Val Tyr Leu Ala Glu Ile
                                25
Asp Arg Val Ala Lys Leu Tyr Arg Leu Asp Thr Tyr Pro His Gln Ile
                           40
Glu Val Ile Thr Ser Glu Gln Met Met Asp Ala Tyr Ser Ser Val Gly
                       55
                                           60
Met Pro Ile Asn Tyr Pro His Trp Ser Phe Gly Lys Lys Phe Ile Glu
                    70
                                       75
Thr Glu Arg Leu Tyr Lys His Gly Gln Gln Gly Leu Ala Tyr Glu Ile
              85
Val Ile Asn Ser Asn Pro Cys Ile Ala Tyr Leu Met Glu Glu Asn Thr
          100
                                105
Ile Thr Met Gln Ala Leu Val Met Ala His Ala Cys Tyr Gly His Asn
                           120
                                               125
```

```
Ser Phe Phe Lys Asn Asn Tyr Leu Phe Arg Ser Trp Thr Asp Ala Ser
           135
                             140
Ser Ile Val Asp Tyr Leu Ile Phe Ala Arg Lys Tyr Ile Thr Glu Cys
                 150
                                     155
Glu Glu Arg Tyr Gly Val Asp Glu Val Glu Arg Leu Leu Asp Ser Cys
                                 170
              165
His Ala Leu Met Asn Tyr Gly Val Asp Arg Tyr Lys Arg Pro Gln Lys
                              185
Ile Ser Leu Gln Glu Glu Lys Ala Arg Gln Lys Ser Arg Glu Glu Tyr
                          200
Leu Gln Ser Gln Val Asn Met Leu Trp Arg Thr Leu Pro Lys Arg Glu
                                         220
                      215
Glu Glu Lys Thr Val Ala Glu Ala Arg Arg Tyr Pro Ser Glu Pro Gln
                  230
                                     235
Glu Asn Leu Leu Tyr Phe Met Glu Lys Asn Ala Pro Leu Leu Glu Ser
                                  250
Trp Gln Arg Glu Ile Leu Arg Ile Val Arg Lys Val Ser Gln Tyr Phe
                             265
           260
Tyr Pro Gln Lys Gln Thr Gln Val Met Asn Glu Gly Trp Ala Thr Phe
                       280
Trp His Tyr Thr Ile Leu Asn His Leu Tyr Asp Glu Gly Lys Val Thr
                      295
Glu Arg Phe Met Leu Glu Phe Leu His Ser His Thr Asn Val Val Phe
                   310
                                     315
Gln Pro Pro Tyr Asn Ser Pro Trp Tyr Ser Gly Ile Asn Pro Tyr Ala
                                 330
              325
Leu Gly Phe Ala Met Phe Gln Asp Ile Lys Arg Ile Cys Gln Ser Pro
                              345
          340
Thr Glu Glu Asp Lys Tyr Trp Phe Pro Asp Ile Ala Gly Ser Asp Trp
                         360
Leu Glu Thr Leu His Phe Ala Met Arg Asp Phe Lys Asp Glu Ser Phe
                     375
                                 380
Ile Ser Gln Phe Leu Ser Pro Lys Val Met Arg Asp Phe Arg Phe Phe
                  390
                                   395
Thr Val Leu Asp Asp Asp Arg His Asn Tyr Leu Glu Ile Ser Ala Ile
                                  410
His Asn Glu Glu Gly Tyr Arg Glu Ile Arg Asn Arg Leu Ser Ser Gln
                              425
Tyr Asn Leu Ser Asn Leu Glu Pro Asn Ile Gln Ile Trp Asn Val Asp
                                              445
                          440
Leu Arg Gly Asp Arg Ser Leu Thr Leu Arg Tyr Ile Pro His Asn Arg
                      455
                                         460
Ala Pro Leu Asp Arg Gly Arg Lys Glu Val Leu Lys His Val His Arg
                   470
                                     475
Leu Trp Gly Phe Asp Val Met Leu Glu Gln Gln Asn Glu Asp Gly Ser
              485
                                 490
Ile Glu Leu Leu Glu Arg Cys Pro Pro Arg Met Gly Asn Leu
                              505
<210> 366
<211> 452
<212> PRT
<213> Escherichia coli
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 Met
 Lys
 Arg
 Leu
 Ser
 Ile
 Thr
 Val
 Arg
 Leu
 Thr
 Leu
 Phe
 Ile
 Leu

 1
 5
 10
 10
 15

 Leu
 Leu
 Ser
 Val
 Ala
 Gly
 Ala
 Gly
 Ile
 Val
 Trp
 Thr
 Leu
 Tyr
 Asn
 Gly

 Leu
 Ala
 Ser
 Glu
 Leu
 Lys
 Trp
 Arg
 Asp
 Asp
 Thr
 Thr
 Leu
 Ile
 Asn
 Arg

```
40
Thr Ala Gln Ile Lys Gln Leu Leu Ile Asp Gly Val Asn Pro Asp Thr
Leu Pro Val Tyr Phe Asn Arg Met Met Asp Val Ser Gln Asp Ile Leu
                  70
Ile Ile His Gly Asp Ser Ile Asn Lys Ile Val Asn Arg Thr Asn Val
                                90
              85
Ser Asp Gly Met Leu Asn Asn Ile Pro Ala Ser Glu Thr Ile Ser Ala
                             105
          100
Ala Gly Ile Tyr Arg Ser Ile Ile Asn Asp Thr Glu Ile Asp Ala Leu
                        120
                                           125
Arg Ile Asn Ile Asp Glu Val Ser Pro Ser Leu Thr Val Thr Val Ala
            135
                              140
Lys Leu Ala Ser Ala Arg His Asn Met Leu Glu Gln Tyr Lys Ile Asn
               150
                                     155
Ser Ile Ile Cys Ile Val Ala Ile Val Leu Cys Ser Val Leu Ser
                                 170
              165
Pro Leu Leu Ile Arg Thr Gly Leu Arg Glu Ile Lys Lys Leu Ser Gly
                             185
           180
Val Thr Glu Ala Leu Asn Tyr Asn Asp Ser Arg Glu Pro Val Glu Val
                         200
Ser Ala Leu Pro Arg Glu Leu Lys Pro Leu Gly Gln Ala Leu Asn Lys
                      215
                                       220
Met His His Ala Leu Val Lys Asp Phe Glu Arg Leu Ser Gln Phe Ala
                  230
                          235
Asp Asp Leu Ala His Glu Leu Arg Thr Pro Ile Asn Ala Leu Leu Gly
                                250
             245
Gln Asn Gln Val Thr Leu Ser Gln Thr Arg Ser Ile Ala Glu Tyr Gln
          260
                              265
Lys Thr Ile Ala Gly Asn Ile Glu Glu Leu Glu Asn Ile Ser Arg Leu
                          280
Thr Glu Asn Ile Leu Phe Leu Ala Arg Ala Asp Lys Asn Asn Val Leu
            295
                                        300
Val Lys Leu Asp Ser Leu Ser Leu Asn Lys Glu Val Glu Asn Leu Leu
                                    315
               310
Asp Tyr Leu Glu Tyr Leu Ser Asp Glu Lys Glu Ile Cys Phe Lys Val
             325 330
Glu Cys Asn Gln Gln Ile Phe Ala Asp Lys Ile Leu Leu Gln Arg Met
                             345
Leu Ser Asn Leu Ile Val Asn Ala Ile Arg Tyr Ser Pro Glu Lys Ser
      355 360
Arg Ile His Ile Thr Ser Phe Leu Asp Thr Asn Ser Tyr Leu Asn Ile
                      375
Asp Ile Ala Ser Pro Gly Thr Lys Ile Asn Glu Pro Glu Lys Leu Phe
                  390
                                     395
Arg Arg Phe Trp Arg Gly Asp Asn Ser Arg His Ser Val Gly Gln Gly
              405
                                 410
Leu Gly Leu Ser Leu Val Lys Ala Ile Ala Glu Leu His Gly Gly Ser
                             425
Ala Thr Tyr His Tyr Leu Asn Lys His Asn Val Phe Arg Ile Thr Leu
       435
Pro Gln Arg Asn
   450
<210> 367
<211> 239
<212> PRT
<213> Escherichia coli
<400> 367
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Met Asn Gln Ala Val Ser Ile Thr Tyr Asp Leu Trp His Ile Ile Phe
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Met Lys Ile Leu Leu Ile Glu Asp Asn Gln Arg Thr Gln Glu Trp Val
                              25
Thr Gln Gly Leu Ser Glu Ala Gly Tyr Val Ile Asp Ala Val Ser Asp
Gly Arg Asp Gly Leu Tyr Leu Ala Leu Lys Asp Asp Tyr Ala Leu Ile
Ile Leu Asp Ile Met Leu Pro Gly Met Asp Gly Trp Gln Ile Leu Gln
                                      75
                   70
Thr Leu Arg Thr Ala Lys Gln Thr Pro Val Ile Cys Leu Thr Ala Arg
                                 90
Asp Ser Val Asp Asp Arg Val Arg Gly Leu Asp Ser Gly Ala Asn Asp
                             105
           100
Tyr Leu Val Lys Pro Phe Ser Phe Ser Glu Leu Leu Ala Arg Val Arg
                                             125
                          120
Ala Gln Leu Arg Gln His His Ala Leu Asn Ser Thr Leu Glu Ile Ser
                      135 . 140
Gly Leu Arg Met Asp Ser Val Ser His Ser Val Ser Arg Asp Asn Ile
                  150
                                      155
Ser Ile Thr Leu Thr Arg Lys Glu Phe Gln Leu Leu Trp Leu Leu Ala
                                  170
              165
Ser Arg Ala Gly Glu Ile Ile Pro Arg Thr Val Ile Ala Ser Glu Ile
                             185
           180
Trp Gly Ile Asn Phe Asp Ser Asp Thr Asn Thr Val Asp Val Ala Ile
                 200
Arg Arg Leu Arg Ala Lys Val Asp Asp Pro Phe Pro Glu Lys Leu Ile
                                         220
                      215
Ala Thr Ile Arg Gly Met Gly Tyr Ser Phe Val Ala Val Lys Lys
<210> 368
<211> 172
<212> PRT
<213> Escherichia coli
<400> 368
Met Ile Leu Lys Ser Ala Ile Ser Ala Asp Ser Leu Leu Ala Lys Asp
                                 10 15
Ala Phe Arg Ala Ser Phe His Leu His Phe Leu Arg Asn His Gly Ile
                               25
Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg Tyr
                         40
        35
Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile Lys
Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala Trp
                   70
                                      75
Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser Lys
                                   90
               85
Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro Gly
                               105
          100
Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys Gln
                           120
Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp Thr
                       135
                                         140
Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys Ile
                                      155
                   150
Ile Lys Ala Tyr Asp Gly Glu Ile Phe Tyr His Arg
```

165

```
<210> 369
<211> 274
<212> PRT
<213> Escherichia coli
<400> 369
Met Thr Glu Phe Thr Thr Leu Leu Gln Gln Gly Asn Ala Trp Phe Phe
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Ile Pro Ser Ala Ile Leu Leu Gly Ala Leu His Gly Leu Glu Pro Gly
His Ser Lys Thr Met Met Ala Ala Phe Ile Ile Ala Ile Lys Gly Thr
                          40
Ile Lys Gln Ala Val Met Leu Gly Leu Ala Ala Thr Ile Ser His Thr
                   55
Ala Val Val Trp Leu Ile Ala Phe Gly Gly Met Val Ile Ser Lys Arg
                                       75
Phe Thr Ala Gln Ser Ala Glu Pro Trp Leu Gln Leu Ile Ser Ala Val
               85
                                   90
Ile Ile Ile Ser Thr Ala Phe Trp Met Phe Trp Arg Thr Trp Arg Gly
                              105
           100
                                                   110
Glu Arg Asn Trp Leu Glu Asn Met His Gly His Asp Tyr Glu His His
                           120
His His Asp His Glu His His His Asp His Gly His His His His
                       135
Glu His Gly Glu Tyr Gln Asp Ala His Ala Arg Ala His Ala Asn Asp
                   150
                                      155
Ile Lys Arg Arg Phe Asp Gly Arg Glu Val Thr Asn Trp Gln Ile Leu
               165
                                  170
Leu Phe Gly Leu Thr Gly Gly Leu Ile Pro Cys Pro Ala Ala Ile Thr
                               185
                                                  190
           180
Val Leu Leu Ile Cys Ile Gln Leu Lys Ala Leu Thr Leu Gly Ala Thr
                           200
Leu Val Val Ser Phe Ser Ile Gly Leu Ala Leu Thr Leu Val Thr Val
                       215
                                           220
Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser
                230
                                      235
Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu
                                  250
Ile Gly Leu Val Gly Val Tyr Met Gly Val His Gly Phe Met Gly Ile
                               265
Met Arg
<210> 370
<211> 82
<212> PRT
<213> Escherichia coli
<400> 370
Met Cys Ile Gly Val Pro Gly Gln Val Leu Ala Val Gly Glu Asp Ile
His Gln Leu Ala Gln Val Glu Val Cys Gly Ile Lys Arg Asp Val Asn
                               25
Ile Ala Leu Ile Cys Glu Gly Asn Pro Ala Asp Leu Leu Gly Gln Trp
                           40
Val Leu Val His Val Gly Phe Ala Met Ser Ile Ile Asp Glu Asp Glu
                       55
                                          60
Ala Lys Ala Thr Leu Asp Ala Leu Arg Gln Met Asp Tyr Asp Ile Thr
65
Ser Ala
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<211> 113
<212> PRT
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<400> 371
Met His Glu Leu Ser Leu Cys Gln Ser Ala Val Glu Ile Ile Gln Arq
1 5
                             10
Gln Ala Glu Gln His Asp Val Lys Arg Val Thr Ala Val Trp Leu Glu
                        25
Ile Gly Ala Leu Ser Cys Val Glu Glu Ser Ala Val Arg Phe Ser Phe
                           45
          40
Glu Ile Val Cys His Gly Thr Val Ala Gln Gly Cys Asp Leu His Ile
 50 55
Val Tyr Lys Pro Ala Gln Ala Trp Cys Trp Asp Cys Ser Gln Val Val
                              75
Glu Ile His Gln His Asp Ala Gln Cys Pro Leu Cys His Gly Glu Arg
           85
                    90
Leu Arg Val Asp Thr Gly Asp Ser Leu Ile Val Lys Ser Ile Glu Val
        100 105
Glu
<210> 372
<211> 162
<212> PRT
<213> Escherichia coli
<400> 372
Met Thr Glu Glu Ile Ala Gly Phe Gln Thr Ser Pro Lys Ala Gln Val
                       10 15
Gln Ala Ala Phe Glu Glu Ile Ala Arg Arg Ser Met His Asp Leu Ser
Phe Leu His Pro Ser Met Pro Val Tyr Val Ser Asp Phe Thr Leu Phe
                             45
 35 40
Glu Gly Gln Trp Thr Gly Cys Val Ile Thr Pro Trp Met Leu Ser Ala
 50 55
Val Ile Phe Pro Gly Pro Asp Gln Leu Trp Pro Leu Arg Lys Val Ser
                70 75 80
Glu Lys Ile Gly Leu Gln Leu Pro Tyr Gly Thr Met Thr Phe Thr Val
                          90
Gly Glu Leu Asp Gly Val Ser Gln Tyr Leu Ser Cys Ser Leu Met Ser
         100 105 110
Pro Leu Ser His Ser Met Ser Ile Glu Glu Gly Gln Arg Leu Thr Asp
 115 120
Asp Cys Ala Arg Met Ile Leu Ser Leu Pro Val Thr Asn Pro Asp Val
 130 135
                        140
Pro His Ala Gly Arg Arg Ala Leu Leu Phe Gly Arg Arg Ser Gly Glu
                150 155
Asn Ala
<210> 373
<211> 164
<212> PRT
<213> Escherichia coli
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<400> 373

Met Arg Ile Leu Val Leu Gly Val Gly Asn Ile Leu Leu Thr Asp Glu Ala Ile Gly Val Arg Ile Val Glu Ala Leu Glu Gln Arg Tyr Ile Leu Pro Asp Tyr Val Glu Ile Leu Asp Gly Gly Thr Ala Gly Met Glu Leu 40 Leu Gly Asp Met Ala Asn Arg Asp His Leu Ile Ile Ala Asp Ala Ile Val Ser Lys Lys Asn Ala Pro Gly Thr Met Met Ile Leu Arg Asp Glu 70 75 Glu Val Pro Ala Leu Phe Thr Asn Lys Ile Ser Pro His Gln Leu Gly 85 90 Leu Ala Asp Val Leu Ser Ala Leu Arg Phe Thr Gly Glu Phe Pro Lys 105 Lys Leu Thr Leu Val Gly Val Ile Pro Glu Ser Leu Glu Pro His Ile 120 Gly Leu Thr Pro Thr Val Glu Ala Met Ile Glu Pro Ala Leu Glu Gln 135 140 Val Leu Ala Ala Leu Arg Glu Ser Gly Val Glu Ala Ile Pro Arg Glu 150 Ala Ile His Asp

<210> 374

<211> 567

<212> PRT

<213> Escherichia coli

<400> 374

Met Ser Gln Arg Ile Thr Ile Asp Pro Val Thr Arg Ile Glu Gly His 10 Leu Arg Ile Asp Cys Glu Ile Glu Asn Gly Val Val Ser Lys Ala Trp 20 25 Ala Ser Gly Thr Met Trp Arg Gly Met Glu Glu Ile Val Lys Asn Arg 40 Asp Pro Arg Asp Ala Trp Met Ile Val Gln Arg Ile Cys Gly Val Cys Thr Thr His Ala Leu Ser Ser Val Arg Ala Ala Glu Ser Ala Leu 70 75 Asn Ile Asp Val Pro Val Asn Ala Gln Tyr Ile Arg Asn Ile Ile Leu 90 85 Ala Ala His Thr Thr His Asp His Ile Val His Phe Tyr Gln Leu Ser 105 Ala Leu Asp Trp Val Asp Ile Thr Ser Ala Leu Gln Ala Asp Pro Thr 120 Lys Ala Ser Glu Met Leu Lys Gly Val Ser Thr Trp His Leu Asn Ser 135 140 Pro Glu Glu Phe Thr Lys Val Gln Asn Lys Ile Lys Asp Leu Val Ala 155 150 Ser Gly Gln Leu Gly Ile Phe Ala Asn Gly Tyr Trp Gly His Pro Ala 170 Met Lys Leu Pro Pro Glu Val Asn Leu Ile Ala Val Ala His Tyr Leu 185 Gln Ala Leu Glu Cys Gln Arg Asp Ala Asn Arg Val Val Ala Leu Leu 200 205 Gly Gly Lys Thr Pro His Ile Gln Asn Leu Ala Val Gly Gly Val Ala 215 220 Asn Pro Ile Asn Leu Asp Gly Leu Gly Val Leu Asn Leu Glu Arg Leu 235 230

Met Tyr Ile Lys Ser Phe Ile Asp Lys Leu Ser Asp Phe Val Glu Gln

250

Val Tyr Lys Val Asp Thr Ala Val Ile Ala Ala Phe Tyr Pro Glu Trp

245 .

```
265
         260
Leu Thr Arg Gly Lys Gly Ala Val Asn Tyr Leu Ser Val Pro Glu Phe
                       280
Pro Thr Asp Ser Lys Asn Gly Ser Phe Leu Phe Pro Gly Gly Tyr Ile
                            300
                   295
Glu Asn Ala Asp Leu Ser Ser Tyr Arg Pro Ile Thr Ser His Ser Asp
                        315
       310
Glu Tyr Leu Ile Lys Gly Ile Gln Glu Ser Ala Lys His Ser Trp Tyr
                     330
      325
Lys Asp Glu Ala Pro Gln Ala Pro Trp Glu Gly Thr Thr Ile Pro Ala
                           345 350
Tyr Asp Gly Trp Ser Asp Asp Gly Lys Tyr Ser Trp Val Lys Ser Pro
                       360 365
Thr Phe Tyr Gly Lys Thr Val Glu Val Gly Pro Leu Ala Asn Met Leu
                     375
                                     380
Val Lys Leu Ala Ala Gly Arg Glu Ser Thr Gln Asn Lys Leu Asn Glu
                390
                                  395
Ile Val Ala Ile Tyr Gln Lys Leu Thr Gly Asn Thr Leu Glu Val Ala
                               410
Gln Leu His Ser Thr Leu Gly Arg Ile Ile Gly Arg Thr Val His Cys
                           425
                                          430
Cys Glu Leu Gln Asp Ile Leu Gln Asn Gln Tyr Ser Ala Leu Ile Thr
                       440
                                         445
Asn Ile Gly Lys Gly Asp His Thr Thr Phe Val Lys Pro Asn Ile Pro
                    455
Ala Thr Gly Glu Phe Lys Gly Val Gly Phe Leu Glu Ala Pro Arg Gly
                 470
                                  475
Met Leu Ser His Trp Met Val Ile Lys Asp Gly Ile Ile Ser Asn Tyr
                     490
             485
Gln Ala Val Val Pro Ser Thr Trp Asn Ser Gly Pro Arg Asn Phe Asn
                           505
         500
Asp Asp Val Gly Pro Tyr Glu Gln Ser Leu Val Gly Thr Pro Val Ala
                       520
Asp Pro Asn Lys Pro Leu Glu Val Val Arg Thr Ile His Ser Phe Asp
 530 , 535
                            540
Pro Cys Met Ala Cys Ala Val His Val Val Asp Ala Asp Gly Asn Glu
      550 555
Val Val Ser Val Lys Val Leu .
             565
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Met Ser His Asp Pro Gln Pro Leu Gly Gly Lys Ile Ile Ser Lys Pro
1
Val Met Ile Phe Gly Pro Leu Ile Val Ile Cys Met Leu Leu Ile Val
                           25
Lys Arg Leu Val Phe Gly Leu Gly Ser Val Ser Asp Leu Asn Gly Gly
               40
                                         45
Phe Pro Trp Gly Val Trp Ile Ala Phe Asp Leu Leu Ile Gly Thr Gly
                     55
                                      60
Phe Ala Cys Gly Gly Trp Ala Leu Ala Trp Ala Val Tyr Val Phe Asn
                 70
Arg Gly Gln Tyr His Pro Leu Val Arg Pro Ala Leu Leu Ala Ser Leu
                               90
```

Phe Gly Tyr Ser Leu Gly Gly Leu Ser Ile Thr Ile Asp Val Gly Arg

```
Tyr Trp Asn Leu Pro Tyr Phe Tyr Ile Pro Gly His Phe Asn Val Asn
                          120
Ser Val Leu Phe Glu Thr Ala Val Cys Met Thr Ile Tyr Ile Gly Val
                      135
Met Ala Leu Glu Phe Ala Pro Ala Leu Phe Glu Arg Leu Gly Trp Lys
               150 155
Val Ser Leu Gln Arg Leu Asn Lys Val Met Phe Phe Ile Ile Ala Leu
                                170
            165
Gly Ala Leu Leu Pro Thr Met His Gln Ser Ser Met Gly Ser Leu Met
          180 185
Ile Ser Ala Gly Tyr Lys Val His Pro Leu Trp Gln Ser Tyr Glu Met
                  200
Leu Pro Leu Phe Ser Leu Leu Thr Ala Phe Ile Met Gly Phe Ser Ile
         215
Val Ile Phe Glu Gly Ser Leu Val Gln Ala Gly Leu Arg Gly Asn Gly
                                  235
                   230
Pro Asp Glu Lys Ser Leu Phe Val Lys Leu Thr Asn Thr Ile Ser Val
                                 250
Leu Leu Ala Ile Phe Ile Val Leu Arg Phe Gly Glu Leu Ile Tyr Arg
                             265
           260
Asp Lys Leu Ser Leu Ala Phe Ala Gly Asp Phe Tyr Ser Val Met Phe
                         280
Trp Ile Glu Val Leu Leu Met Leu Phe Pro Leu Val Val Leu Arg Val
                     295
                                        300
Ala Lys Leu Arg Asn Asp Ser Arg Met Leu Phe Leu Ser Ala Leu Ser
                              315
                  310
Ala Leu Leu Gly Cys Ala Thr Trp Arg Leu Thr Tyr Ser Leu Val Ala
                                  330
               325
Phe Asn Pro Gly Gly Gly Tyr Ala Tyr Phe Pro Thr Trp Glu Glu Leu
           340
                              345
Leu Ile Ser Ile Gly Phe Val Ala Ile Glu Ile Cys Ala Tyr Ile Val
                       360
                                            365
Leu Ile Arg Leu Leu Pro Ile Leu Pro Pro Leu Lys Gln Asn Asp His
            375
Asn Arg His Glu Ala Ser Lys Ala
<210> 376
<211> 328
<212> PRT
<213> Escherichia coli
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Met Asn Arg Arg Asn Phe Ile Lys Ala Ala Ser Cys Gly Ala Leu Leu
                                  10
                                                 · 15
Thr Gly Ala Leu Pro Ser Val Ser His Ala Ala Ala Glu Asn Arg Pro
                              25
Pro Ile Pro Gly Ser Leu Gly Met Leu Tyr Asp Ser Thr Leu Cys Val
                          40
Gly Cys Gln Ala Cys Val Thr Lys Cys Gln Asp Ile Asn Phe Pro Glu
Arg Asn Pro Gln Gly Glu Gln Thr Trp Ser Asn Asn Asp Lys Leu Ser
                                     75
Pro Tyr Thr Asn Asn Ile Ile Gln Val Trp Thr Ser Gly Thr Gly Val
                                 90
Asn Lys Asp Gln Glu Glu Asn Gly Tyr Ala Tyr Ile Lys Lys Gln Cys
                             105
                                               110
Met His Cys Val Asp Pro Asn Cys Val Ser Val Cys Pro Val Ser Ala
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120
Leu Lys Lys Asp Pro Lys Thr Gly Ile Val His Tyr Asp Lys Asp Val
                              140
                   135
Cys Thr Gly Cys Arg Tyr Cys Met Val Ala Cys Pro Tyr Asn Val Pro
                                 155
               150
Lys Tyr Asp Tyr Asn Asn Pro Phe Gly Ala Leu His Lys Cys Glu Leu
                    170
Cys Asn Gln Lys Gly Val Glu Arg Leu Asp Lys Gly Gly Leu Pro Gly
                 185
Cys Val Glu Val Cys Pro Ala Gly Ala Val Ile Phe Gly Thr Arg Glu
                        200
Glu Leu Met Ala Glu Ala Lys Lys Arg Leu Ala Leu Lys Pro Gly Ser
                                     220
                    215
Glu Tyr His Tyr Pro Arg Gln Thr Leu Lys Ser Gly Asp Thr Tyr Leu
                230
                                  235
His Thr Val Pro Lys Tyr Tyr Pro His Leu Tyr Gly Glu Lys Glu Gly
             245
                              250
Gly Gly Thr Gln Val Leu Val Leu Thr Gly Val Pro Tyr Glu Asn Leu
                          265
Asp Leu Pro Lys Leu Asp Asp Leu Ser Thr Gly Ala Arg Ser Glu Asn
                      280
                              285
Ile Gln His Thr Leu Tyr Lys Gly Met Met Leu Pro Leu Ala Val Leu
                  295 300
Ala Gly Leu Thr Val Leu Val Arg Arg Asn Thr Lys Asn Asp His His
      310
                         315
Asp Gly Gly Asp Asp His Glu Ser
             325
<210> 377
<211> 824
<212> PRT
<213> Escherichia coli
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Met Leu Gln Cys Gly Ala Lys Asn Val Asn Pro Leu Glu Arg Phe Val
                              10
Ser Ser Leu Pro Val Ala Ala Val Leu Pro Glu Leu Leu Thr Ala Leu
                    25
Asp Cys Ala Pro Gln Val Leu Leu Ser Ala Pro Thr Gly Ala Gly Lys
              40
Ser Thr Trp Leu Pro Leu Gln Leu Leu Ala His Pro Gly Ile Asn Gly
                     55
Lys Ile Ile Leu Leu Glu Pro Arg Arg Leu Ala Ala Arg Asn Val Ala
                 70
                                  75
Gln Arg Leu Ala Glu Leu Leu Asn Glu Lys Pro Gly Asp Thr Val Gly
             85
                               90
Tyr Arg Met Arg Ala Gln Asn Cys Val Gly Pro Asn Thr Arg Leu Glu
          100 105
Val Val Thr Glu Gly Val Leu Thr Arg Met Ile Gln Arg Asp Pro Glu
      115 120 125
Leu Ser Gly Val Gly Leu Val Ile Leu Asp Glu Phe His Glu Arg Ser
                                     140
                    135
Leu Gln Ala Asp Leu Ala Leu Ala Leu Leu Leu Asp Val Gln Gln Gly
                150 · 155
Leu Arg Asp Asp Leu Lys Leu Leu Ile Met Ser Ala Thr Leu Asp Asn
             165 170
                                                175
Asp Arg Leu Gln Gln Met Leu Pro Glu Ala Pro Val Val Ile Ser Glu
         180
                           185 190
Gly Arg Ser Phe Pro Val Glu Arg Arg Tyr Leu Pro Leu Pro Ala His
```

205

200

Gln Gln Arg Ser Gln Gln Leu Leu Lys Arg Leu Asn Val Arg Gly Gly 485	Gln	Arg	Phe	Asp	Asp	Ala	Val	Ala	Val	Ala	Thr	Ala	Glu	Met	Leu	Arg
240   241   242   245			_			_		_	_,	_	_					
Leu Cys Pro   Leu Tyr   Gly Ala   Leu   Sec   Fu   Ash   A		Glu	Ser	Gly	Ser		Leu	Leu	Pne	Leu		GTÀ	Val	GIŸ	GIU	
11e   Leu   Pro   Ala   Pro   Sin   Gly   Met   Arg   Lev   Sta   Leu   Ala   The   Asan   275   285	Gln	Arg	Val	Gln		Gln	Leu	Ala	Ser		Ile	Gly	Ser	Asp		Leu
275		-		260					265					270		
290   295   300   310	Ile	Leu		Ala	Pro	Gln	Gly		Arg	Lys	Val	Val		Ala	Thr	Asn
310		290					295					300				
Secondary   Seco	305					310					315					320
The color of the	-				325					330					335	
Ser	_	_		340					345					350		
Ser	_		355					360					365			
385		370	_				375					380				
Leu   Leu   Ala   Ala   Lys   Arg   Leu   Leu   Gho   Met   Leu   Gho   Ala   Ceu   Gho   Gho   Gho   Ala   Ala		Asp	Pro	Ala	Gln		Ser	Trp	Leu	Asp		Pro	Pro	Val	Val	
Pro   Arg   Leu   Ala   Ala   Met   Leu   Val   Ser   Ala   Lys   Asn   Asp   Asp   Glu   Ala   Ala		Leu	Ala	Ala		Arg	Leu	Leu	Gln		Leu	Gly	Ala	Leu		Gly
Ala Thr Ala Ala Lys IIe Ala Ala Phe Glu Glu Pro Pro Arg Met 455		-		420					425					430		
Signature   Sign			435					440					445			
465		450					455					460				
Gln Gln Arg Ser Gln Gln Leu Leu Ly Arg Leu Asn Val Arg Gly Gly 495   Glu Ala Asp Ser Ser Ser Leu IIe Ala Pro Leu Leu Ly Arg Gly Gly A96   Asp Arg IIe Ala Arg Arg Arg Gly Gln Asp Gly Arg Tyr Gln Leu Ala 510   Asp Gly Met Gly Ala Met Leu Asp Sys Ala Leu Ser Arg His 535   Glu Trp Leu IIe Ala Pro Leu Leu Leu Leu Gln Gly Gly Sys   Arg IIe Ala Pro Sys		Asn	Ser	Asp	Leu	_	Val	Ala	Phe	Ser	_	Asn	Gln	Pro	Ala	Trp 480
Asp Arg Ile Ala Arg Arg Arg Gly Gln Asp Gly Arg Tyr Gln Leu Ala 515  Asn Gly Met Gly Ala Met Leu Asp Arg Eleu Gln Gly Ser Ala Leu Ser Arg His 530  Glu Trp Leu Ile Ala Pro Leu Leu Leu Gln Gly Ser Ala Ser Pro Asp 545  Ala Arg Ile Leu Leu Ala Leu Val Gln Ser S55  Arg Cys Pro Gln Leu Val Gln Gln Ser S55  Ala Gly Thr Leu Lys Ala Trp Arg Arg Leu Gln Gly Ser Ala Ser Pro Asp 580  Ala Gln Gly Thr Leu Lys Ala Trp Arg Arg Leu Gln Ile Gly Gly Ser S90  Thr Val Lys Val Gln Pro Leu Ala Lys Arg Arg Leu Gln Ile Gly Gln Leu Gln Gly Gln Leu Gln Gly Trp Asp 610  Gln Ala Met Leu Asn Gly Ile Arg Arg Leu Gln Ile Gly Gln Leu Asn 625  Trp Thr Ala Glu Ala Glu Gln Gly Ile Arg Arg Leu Gly Leu Ser Val Leu Asn 625  Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu Glo Leu Gfo	Gln	Gln	Arg	Ser		Gln	Leu	Leu	Lys		Leu	Asn	Val	Arg		Gly
Asn       Gly       Met       Gly       Ala       Met       Leu       Asp       Ala       Asp       Ala       Asp       Ala       Leu       Ser       Arg       His         530	Glu	Ala	Asp		Ser	Leu	Ile	Ala		Leu	Leu	Ala	Gly		Phe	Ala
Glu       Trp       Leu       Ile       Ala       Pro       Leu       Leu       Leu       Gln       Gly       Ser       Ala       Ser       Pro       Asp         545	-	_	515		_	_	_	520					525			
545       556       550       555       560         Ala Arg Ile Leu Leu Leu Leu Leu Leu Sin 565       11e Asp Ile Asp Glu Leu Val Gln 575       560         Arg Cys Pro Gln Leu Val Gln Gln 580       570       570       570         Ala Gln Gly Thr Leu Lys Ala Trp 585       585       580       580         Thr Val Lys Val Gln Pro 600       600       600       605         Thr Val Lys Val Gln Pro 615       615       620       620         Gln Ala Met Leu Asn 610       615       620       635       640         Trp Thr Ala Glu Ala Glu Gln Leu Arg Leu Arg Leu Arg Leu Cys Ala Ala 645       630       630       630       630       640         Lys Trp Leu Pro 660       770 <t< td=""><td></td><td>530</td><td></td><td>_</td><td></td><td></td><td>535</td><td></td><td></td><td></td><td></td><td>540</td><td></td><td></td><td></td><td></td></t<>		530		_			535					540				
Arg Cys Pro Gln Leu Val Gln Gln Ser Asp Thr Val Glu Trp Asp Asp 590  Ala Gln Gly Thr Leu Lys Ala Trp Arg Arg Leu Gln Ile Gly Gln Leu 605  Thr Val Lys Val Gln Pro Leu Ala Lys Pro Ser Glu Asp Glu Leu His 610  Gln Ala Met Leu Asn Gly Ile Arg Asp Lys Gly Leu Ser Val Leu Asn 625  Trp Thr Ala Glu Ala Glu Gln Leu Gln Leu Arg Leu Arg Leu Gln Leu Gln Leu Asn 645  Trp Thr Ala Glu Ala Glu Gln Leu Arg Asp Lys Gly Leu Ser Val Leu Asn 645  Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu 665  Leu Ala Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His		-	Leu	Ile	Ala								Ala	Ser	Pro	
Ala Gln Gly Thr Leu Lys Ala Trp Arg Arg Leu Gln Ile Gly Gln Leu 605  Thr Val Lys Val Gln Pro Leu Ala Lys Pro Ser Glu Asp Glu Leu His 610  Gln Ala Met Leu Asn Gly Ile Arg Asp Lys Gly Leu Ser Val Leu Asn 625  Trp Thr Ala Glu Ala Glu Gln Leu Arg Leu Arg Leu Arg Leu Cys Ala Ala 645  Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu 660  Leu Ala Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His	Ala	Arg	Ile	Leu		Ala	Leu	Leu	Val		Ile	Asp	Glu	Leu		Gln
Thr Val Lys Val Gln Pro Leu Ala Lys Pro Ser Glu Asp Glu Leu His 610  Gln Ala Met Leu Asn Gly Ile Arg Asp Lys Gly Leu Ser Val Leu Asn 625  Trp Thr Ala Glu Ala Glu Gln Leu Arg Leu Arg Leu Arg Leu Cys Ala Ala 645  Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu 660  Leu Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His	_	_		580					585					590		
610			595					600					605			
625		610	-				615					620				
Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu 660 665 670  Leu Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His		Ala	Met	Leu	Asn		Ile	Arg	Asp	Lys		Leu	Ser	Val	Leu	Asn 640
Lys Trp Leu Pro Glu Tyr Asp Trp Pro Ala Val Asp Asp Glu Ser Leu 660 665 670  Leu Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His		Thr	Ala	Glu		Glu	Gln	Leu	Arg		Arg	Leu	Leu	Cys		Ala
Leu Ala Ala Leu Glu Thr Trp Leu Leu Pro His Met Thr Gly Val His	Lys	Trp	Leu			Tyr	Asp	Trp			Val	Asp	Asp			Leu
	Leu	Ala		Leu	Glu	Thr	Trp		Leu	Pro	His	Met		Gly	Val	His

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Ser Leu Arg Gly Leu Lys Ser Leu Asp Ile Tyr Gln Ala Leu Arg Gly
                    695
Leu Leu Asp Trp Gly Met Gln Gln Arg Leu Asp Ser Glu Leu Pro Ala
                              715
                710
His Tyr Thr Val Pro Thr Gly Ser Arg Ile Ala Ile Arg Tyr His Glu
Asp Asn Pro Pro Ala Leu Ala Val Arg Met Gln Glu Met Phe Gly Glu
  740 745
Ala Thr Asn Pro Thr Ile Ala Gln Gly Arg Val Pro Leu Val Leu Glu
              760
Leu Leu Ser Pro Ala Gln Arg Pro Leu Gln Ile Thr Arg Asp Leu Ser
 770 775
Asp Phe Trp Lys Gly Ala Tyr Arg Glu Val Gln Lys Glu Met Lys Gly
      790
                                  795
Arg Tyr Pro Lys His Val Trp Pro Asp Asp Pro Ala Asn Thr Ala Pro
                              810
Thr Arg Arg Thr Lys Lys Tyr Ser
          820
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<211> 316
<212> PRT
<213> Escherichia coli
Met Ser Lys Leu Asp Thr Phe Ile Gln His Ala Val Asn Ala Val Pro
           5 10
Val Ser Gly Thr Ser Leu Ile Ser Ser Leu Tyr Gly Asp Ser Leu Ser
          20
                            25
His Arg Gly Gly Glu Ile Trp Leu Gly Ser Leu Ala Ala Leu Leu Glu
                        40
Gly Leu Gly Phe Gly Glu Arg Phe Val Arg Thr Ala Leu Phe Arg Leu
                    55
Asn Lys Glu Gly Trp Leu Asp Val Ser Arg Ile Gly Arg Arg Ser Phe
                                  75
                70
Tyr Ser Leu Ser Asp Lys Gly Leu Arg Leu Thr Arg Arg Ala Glu Ser
Lys Ile Tyr Arg Ala Glu Gln Pro Ala Trp Asp Gly Lys Trp Leu Leu
                    105 110
Leu Leu Ser Glu Gly Leu Asp Lys Ser Thr Leu Ala Asp Val Lys Lys
                120 125
Gln Leu Ile Trp Gln Gly Phe Gly Ala Leu Ala Pro Ser Leu Met Ala
                    135
                                     140
Ser Pro Ser Gln Lys Leu Ala Asp Val Gln Thr Leu Leu His Glu Ala
                150
                                  155
Gly Val Ala Asp Asn Val Ile Cys Phe Glu Ala Gln Ile Pro Leu Ala
             165 . 170 175
Leu Ser Arg Ala Ala Leu Arg Ala Arg Val Glu Glu Cys Trp His Leu
          180
                           185
Thr Glu Gln Asn Ala Met Tyr Glu Thr Phe Ile Gln Ser Phe Arg Pro
                       200
Leu Val Pro Leu Leu Lys Glu Ala Ala Asp Glu Leu Thr Pro Glu Arg
                                    220
                    215
Ala Phe His Ile Gln Leu Leu Leu Ile His Phe Tyr Arg Arg Val Val
                230
                                 235
Leu Lys Asp Pro Leu Leu Pro Glu Glu Leu Leu Pro Ala His Trp Ala
             245 250
                                               255
Gly His Thr Ala Arg Gln Leu Cys Ile Asn Ile Tyr Gln Arg Val Ala
          260 265 270
Pro Ala Ala Leu Ala Phe Val Ser Glu Lys Gly Glu Thr Ser Val Gly
```

```
280
       275
                                               285
Glu Leu Pro Ala Pro Gly Ser Leu Tyr Phe Gln Arg Phe Gly Gly Leu
                      295
Asn Ile Glu Gln Glu Ala Leu Cys Gln Phe Ile Arg
                   310
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<211> 196
<212> PRT
<213> Escherichia coli
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Met Pro Ile Tyr Gln Ile Asp Gly Leu Thr Pro Val Val Pro Glu Glu
                          10
Ser Phe Val His Pro Thr Ala Val Leu Ile Gly Asp Val Ile Leu Gly
                               25
Lys Gly Val Tyr Val Gly Pro Asn Ala Ser Leu Arg Gly Asp Phe Gly
                           40
Arg Ile Val Val Lys Asp Gly Ala Asn Ile Gln Asp Asn Cys Val Met
                      55
His Gly Phe Pro Glu Gln Asp Thr Val Val Gly Glu Asp Gly His Ile
                  70
                                      75
Gly His Ser Ala Ile Leu His Gly Cys Ile Ile Arg Arg Asn Ala Leu
                                   90
Val Gly Met Asn Ala Val Val Met Asp Gly Ala Val Ile Gly Glu Asn
                               105
           100
Ser Ile Val Gly Ala Ser Ala Phe Val Lys Ala Lys Ala Glu Met Pro
                          120
                                              125
Ala Asn Tyr Leu Ile Val Gly Ser Pro Ala Lys Ala Ile Arg Glu Leu
                       135
                                           140
Ser Glu Gln Glu Leu Ala Trp Lys Lys Gln Gly Thr His Glu Tyr Gln
                   150
                                      155
Val Leu Val Thr Arg Cys Lys Gln Thr Leu His Gln Val Glu Pro Leu
                                170
               165
Arg Glu Ile Glu Pro Gly Arg Lys Arg Leu Val Phe Asp Glu Asn Leu
          180
Arg Pro Lys Gln
      195
<210> 380
<211> 426
<212> PRT
<213> Escherichia coli
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                                   10
Asn Gly Ile Tyr Ala Val Cys Ser Ala His Pro Leu Val Leu Glu Ala
                               25
            20
Ala Ile Arg Tyr Ala Ser Ala Asn Gln Thr Pro Leu Leu Ile Glu Ala
                           40
Thr Ser Asn Gln Val Asp Gln Phe Gly Gly Tyr Thr Gly Met Thr Pro
                        55
                                           60
Ala Asp Phe Arg Gly Phe Val Cys Gln Leu Ala Asp Ser Leu Asn Phe
                   70
                                       75
Pro Gln Asp Ala Leu Ile Leu Gly Gly Asp His Leu Gly Pro Asn Arg
                                   90
               85
Trp Gln Asn Leu Pro Ala Ala Gln Ala Met Ala Asn Ala Asp Asp Leu
                            105
Ile Lys Ser Tyr Val Ala Ala Gly Phe Lys Lys Ile His Leu Asp Cys
```

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125
                         120
      115
Ser Met Ser Cys Gln Asp Asp Pro Ile Pro Leu Thr Asp Asp Ile Val
                                     140
                     135
Ala Glu Arg Ala Ala Arg Leu Ala Lys Val Ala Glu Glu Thr Cys Leu
                                   155
                 150
Glu His Phe Gly Glu Ala Asp Leu Glu Tyr Val Ile Gly Thr Glu Val
                       170
             165
Pro Val Pro Gly Gly Ala His Glu Thr Leu Ser Glu Leu Ala Val Thr
                  185
Thr Pro Asp Ala Ala Arg Ala Thr Leu Glu Ala His Arg His Ala Phe
               200
                                            205
Glu Lys Gln Gly Leu Asn Ala Ile Trp Pro Arg Ile Ile Ala Leu Val
            215
                                        220
Val Gln Pro Gly Val Glu Phe Asp His Thr Asn Val Ile Asp Tyr Gln
                                    235
               230
Pro Ala Lys Ala Ser Ala Leu Ser Gln Met Val Glu Asn Tyr Glu Thr
                                 250
              245
Leu Ile Phe Glu Ala His Ser Thr Asp Tyr Gln Thr Pro Gln Ser Leu
                             265
Arg Gln Leu Val Ile Asp His Phe Ala Ile Leu Lys Val Gly Pro Ala
                         280
                                           285
Leu Thr Phe Ala Leu Arg Glu Ala Leu Phe Ser Leu Ala Ala Ile Glu
                                       300
                     295
Glu Glu Leu Val Pro Ala Lys Ala Cys Ser Gly Leu Arg Gln Val Leu
                 310
                                    315
Glu Asp Val Met Leu Asp Arg Pro Glu Tyr Trp Gln Ser His Tyr His
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Gly Asp Gly Asn Ala Arg Arg Leu Ala Arg Gly Tyr Ser Tyr Ser Asp
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                             345
Arg Val Arg Tyr Tyr Trp Pro Asp Ser Gln Ile Asp Asp Ala Phe Ala
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His Leu Val Arg Asn Leu Ala Asp Ser Pro Ile Pro Leu Pro Leu Ile
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Ser Gln Tyr Leu Pro Leu Gln Tyr Val Lys Val Arg Ser Gly Glu Leu
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Gln Pro Thr Pro Arg Glu Leu Ile Ile Asn His Ile Gln Asp Ile Leu
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           20
Gln Trp Val Gly Phe Ala Gly Ala Asn Leu Val Leu Val Ala Asn Asp
                                   45
                       4.0
Glu Val Ala Glu Asp Pro Val Gln Gln Asn Leu Met Glu Met Val Leu
                      55
                                        60
Ala Glu Gly Ile Ala Val Arg Phe Trp Thr Leu Gln Lys Val Ile Asp
                                    75
                  70
Asn Ile His Arg Ala Ala Asp Arg Gln Lys Ile Leu Leu Val Cys Lys
                                 90
              85
Thr Pro Ala Asp Phe Leu Thr Leu Val Lys Gly Gly Val Pro Val Asn
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           100
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Arg Ile Asn Val Gly Asn Met His Tyr Ala Asn Gly Lys Gln Gln Ile 120 Ala Lys Thr Val Ser Val Asp Ala Gly Asp Ile Ala Ala Phe Asn Asp 135 140 Leu Lys Thr Ala Gly Val Glu Cys Phe Val Gln Gly Val Pro Thr Glu 150 155 Pro Ala Val Asp Leu Phe Lys Leu Leu 165 <210> 382 <211> 133 <212> PRT <213> Escherichia coli <400> 382 Met Glu Ile Ser Leu Leu Gln Ala Phe Ala Leu Gly Ile Ile Ala Phe 10 Ile Ala Gly Leu Asp Met Phe Asn Gly Leu Thr His Met His Arg Pro 25 Val Val Leu Gly Pro Leu Val Gly Leu Val Leu Gly Asp Leu His Thr 45 40 Gly Ile Leu Thr Gly Gly Thr Leu Glu Leu Val Trp Met Gly Leu Ala 55 Pro Leu Ala Gly Ala Gln Pro Pro Asn Val Ile Ile Gly Thr Ile Val Gly Thr Ala Phe Ala Ile Thr Thr Gly Val Lys Pro Asp Val Ala Val 90 85 Gly Val Ala Val Pro Phe Ala Val Ala Val Gln Met Gly Ile Thr Phe 105 100 Leu Phe Ser Val Met Ser Gly Val Met Ser Arg Cys Asp Leu Ala Thr 120 115 Asn Pro Arg Arg Ile 130 <210> 383 <211> 167 <212> PRT <213> Escherichia coli <400> 383 Met His Cys Tyr Asn Gly Met Thr Gly Leu His His Arg Glu Pro Gly 10 Met Val Gly Ala Gly Leu Thr Asp Lys Arg Ala Trp Leu Glu Leu Ile 25 Ala Asp Gly His His Val His Pro Ala Ala Met Ser Leu Cys Cys 40 Cys Ala Lys Glu Arg Ile Val Leu Ile Thr Asp Ala Met Gln Ala Ala 55 60 Gly Met Pro Asp Gly Arg Tyr Thr Leu Cys Gly Glu Glu Val Gln Met 75 70 His Gly Gly Val Val Arg Thr Ala Ser Gly Gly Leu Ala Gly Ser Thr 90 85 Leu Ser Val Asp Ala Ala Val Arg Asn Met Val Glu Leu Thr Gly Val 105 Thr Pro Ala Glu Ala Ile His Met Ala Ser Leu His Pro Ala Arg Met 120 125 Leu Gly Val Asp Gly Val Leu Gly Ser Leu Lys Pro Gly Lys Arg Ala 140 135 Arg Val Val Ala Leu Asp Ser Gly Leu His Val Gln Gln Ile Trp Ile 155

Gln Gly Gln Leu Ala Ser Phe 165

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375

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Val Arg Gly Gln Arg Thr Lys Thr Asn Ala Arg Thr Arg Lys Gly Pro

110 100 105 Arg Lys Pro Ile Lys Lys <210> 387 <211> 129 <212> PRT <213> Escherichia coli <400> 387 Met Ala Lys Ala Pro Ile Arg Ala Arg Lys Arg Val Arg Lys Gln Val 10 Ser Asp Gly Val Ala His Ile His Ala Ser Phe Asn Asn Thr Ile Val Thr Ile Thr Asp Arg Gln Gly Asn Ala Leu Gly Trp Ala Thr Ala Gly 40 45 Gly Ser Gly Phe Arg Gly Ser Arg Lys Ser Thr Pro Phe Ala Ala Gln 55 Val Ala Ala Glu Arg Cys Ala Asp Ala Val Lys Glu Tyr Gly Ile Lys Asn Leu Glu Val Met Val Lys Gly Pro Gly Pro Gly Arg Glu Ser Thr 90 Ile Arg Ala Leu Asn Ala Ala Gly Phe Arg Ile Thr Asn Ile Thr Asp 105 110 Val Thr Pro Ile Pro His Asn Gly Cys Arg Pro Pro Lys Lys Arg Arg 120 Val <210> 388 <211> 206 <212> PRT <213> Escherichia coli <400> 388 Met Ala Arg Tyr Leu Gly Pro Lys Leu Lys Leu Ser Arg Arg Glu Gly Thr Asp Leu Phe Leu Lys Ser Gly Val Arg Ala Ile Asp Thr Lys Cys 25 Lys Ile Glu Gln Ala Pro Gly Gln His Gly Ala Arg Lys Pro Arg Leu 4.5 Ser Asp Tyr Gly Val Gln Leu Arg Glu Lys Gln Lys Val Arg Arg Ile Tyr Gly Val Leu Glu Arg Gln Phe Arg Asn Tyr Tyr Lys Glu Ala Ala 70 75 Arg Leu Lys Gly Asn Thr Gly Glu Asn Leu Leu Ala Leu Leu Glu Gly 90 Arg Leu Asp Asn Val Val Tyr Arg Met Gly Phe Gly Ala Thr Arg Ala 105 110 Glu Ala Arg Gln Leu Val Ser His Lys Ala Ile Met Val Asn Gly Arg 120 Val Val Asn Ile Ala Ser Tyr Gln Val Ser Pro Asn Asp Val Val Ser 135 140 Ile Arg Glu Lys Ala Lys Lys Gln Ser Arg Val Lys Ala Ala Leu Glu 150 155 Leu Ala Glu Gln Arg Glu Lys Pro Thr Trp Leu Glu Val Asp Ala Gly 170 165 Lys Met Glu Gly Thr Phe Lys Arg Lys Pro Glu Arg Ser Asp Leu Ser

180 185 190
Ala Asp Ile Asn Glu His Leu Ile Val Glu Leu Tyr Ser Lys

205

200

195

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Arg Gln Ala Met Phe Arg Asn Met Ala Gly Ser Leu Val Arg His Glu

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Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg
                      55
Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe
                                    75
                   70
Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg
Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr
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Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu
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Ala Leu Ile Phe Trp Leu Pro Tyr Ser Gln Pro Leu Phe Ala Ala Leu
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Phe Pro Gln Leu Pro Arg Pro Val Tyr Gln Gln Glu Ser Phe Ala Ala
Leu Ala Leu Ala His Phe Trp Leu Val Gly Ile Ser Ser Leu Phe Ala
                       55
Val Ile Ile Gly Thr Gly Ala Gly Ile Ala Val Thr Arg Pro Trp Gly
                                       75
Ala Glu Phe Arg Pro Leu Val Glu Thr Ile Ala Ala Val Gly Gln Thr
                                   90
Phe Pro Pro Val Ala Val Leu Ala Ile Ala Val Pro Val Ile Gly Phe
                               105
Gly Leu Gln Pro Ala Ile Ile Ala Leu Ile Leu Tyr Gly Val Leu Pro
                                              125
                          120
Val Leu Gln Ala Thr Leu Ala Gly Leu Gly Ala Ile Asp Ala Ser Val
                                          140
                      135
Thr Glu Val Ala Lys Gly Met Gly Met Ser Arg Gly Gln Arg Val Arg
                                       155
                  150
Lys Val Glu Leu Pro Leu Ala Ala Pro Val Ile Leu Ala Gly Val Arg
               165
                                   170
Thr Ser Val Ile Ile Asn Ile Gly Thr Ala Thr Ile Ala Ser Thr Val
                               185
Gly Ala Ser Thr Leu Gly Thr Pro Ile Ile Ile Gly Leu Ser Gly Phe
                           200
Asn Thr Ala Tyr Val Ile Gln Gly Ala Leu Leu Val Ala Leu Ala Ala
                                           220
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Ile Ile Ala Asp Arg Leu Phe Glu Arg Leu Val Gln Ala Leu Ser Gln
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                                       235
His Ala Lys
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Met Ile Glu Phe Ser His Val Ser Lys Leu Phe Gly Ala Gln Lys Ala
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Ile Gly Thr Ser Gly Ser Gly Lys Ser Thr Thr Leu Lys Met Ile Asn
                           40
Arg Leu Val Glu His Asp Ser Gly Glu Ile Arg Phe Ala Gly Glu Glu
Ile Arg Ser Leu Pro Val Leu Glu Leu Arg Arg Arg Met Gly Tyr Ala
                   70
Ile Gln Ser Ile Gly Leu Phe Pro His Trp Ser Val Ala Gln Asn Ile
                                  90
               85
Ala Thr Val Pro Gln Leu Gln Lys Trp Ser Arg Ala Arg Ile Asp Asp
                              105
           100
Arg Ile Asp Glu Leu Met Ala Leu Leu Gly Leu Glu Ser Asn Leu Arg
                          120
                                              125
Glu Arg Tyr Pro His Gln Leu Ser Gly Gly Gln Gln Gln Arg Val Gly
                      135
                                          140
Val Ala Arg Ala Leu Ala Ala Asp Pro Gln Val Leu Leu Met Asp Glu
           150
                                       155
Pro Phe Gly Ala Leu Asp Pro Val Thr Arg Gly Ala Leu Gln Glu
                                   170
Met Thr Arg Ile His Arg Leu Leu Gly Arg Thr Ile Val Leu Val Thr
                               185
His Asp Ile Asp Glu Ala Leu Arg Leu Ala Glu His Leu Val Leu Met
                           200
Asp His Gly Glu Val Val Gln Gln Gly Asn Pro Leu Thr Met Leu Thr
                                           220
                       215
Arg Pro Ala Asn Asp Phe Val Arg Gln Phe Phe Gly Arg Ser Glu Leu
                  230
                                       235
Gly Val Arg Leu Leu Ser Leu Arg Ser Val Ala Asp Tyr Val Arg Arg
                                  250
               245
Glu Glu Arg Ala Asp Gly Glu Ala Leu Ala Glu Glu Met Thr Leu Arg
           260
                               265
Asp Ala Leu Ser Leu Phe Val Ala Arg Gly Cys Glu Val Leu Pro Val
                           280
                                              285
Val Asn Met Gln Gly Gln Pro Cys Gly Thr Leu His Phe Gln Asp Leu
                      295
Leu Val Glu Ala
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Met Thr Tyr Phe Arg Ile Asn Pro Val Leu Ala Leu Leu Leu Leu
Thr Ala Ile Ala Ala Ala Leu Pro Phe Ile Ser Tyr Ala Pro Asn Arg
                                25
Leu Val Ser Gly Glu Gly Arg His Leu Trp Gln Leu Trp Pro Gln Thr
                            40
Ile Trp Met Leu Val Gly Val Gly Cys Ala Trp Leu Thr Ala Cys Phe
Ile Pro Gly Lys Lys Gly Ser Ile Cys Ala Leu Ile Leu Ala Gln Phe
Val Phe Val Leu Leu Val Trp Gly Ala Gly Lys Ala Ala Thr Gln Leu
                                   90
Ala Gln Asn Gly Ser Ala Leu Ala Arg Thr Ser Leu Gly Ser Gly Phe
                                105
            100
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Trp Leu Ala Ala Ala Leu Ala Leu Leu Ala Cys Ser Asp Ala Ile Arg
                              125
            120
  115
Arg Ile Ser Thr His Pro Leu Trp Arg Trp Leu Leu His Met Gln Ile
                                140
                   135
Ala Ile Ile Pro Leu Trp Leu Leu Tyr Ser Gly Thr Leu Asn Asp Leu
         150 155
Ser Leu Met Lys Glu Tyr Ala Asn Arg Gln Asp Val Phe Asp Asp Ala
                               170
           165
Leu Ala Gln His Leu Thr Leu Leu Phe Gly Ala Val Leu Pro Ala Leu
   180
                            185
Val Ile Gly Val Pro Leu Gly Ile Trp Cys Tyr Phe Ser Thr Ala Arg
                        200
Gln Gly Ala Ile Phe Ser Leu Leu Asn Val Ile Gln Thr Val Pro Ser
                                     220
           215
Val Ala Leu Phe Gly Leu Leu Ile Ala Pro Leu Ala Ala Leu Val Thr
                 230
Ala Phe Pro Trp Leu Gly Thr Leu Gly Ile Ala Gly Thr Gly Met Thr
                               250
Pro Ala Leu Ile Ala Leu Val Leu Tyr Ala Leu Leu Pro Leu Val Arg
                  265 .
Gly Val Val Val Gly Leu Asn Gln Ile Pro Arg Asp Val Leu Glu Ser
              280
Ala Arg Ala Met Gly Met Ser Gly Ala Gln Arg Phe Leu His Val Gln
  290 . 295
                                      . 300
Leu Pro Leu Ala Leu Pro Val Phe Leu Arg Ser Leu Arg Val Val Met
                                  315
                 310
Val Gln Thr Val Gly Met Ala Val Ile Ala Ala Leu Ile Gly Ala Gly
                               330
             325
Gly Phe Gly Ala Leu Val Phe Gln Gly Leu Leu Ser Ser Ala Ile Asp
                  345
          340
Leu Val Leu Leu Gly Val Ile Pro Val Ile Val Leu Ala Val Leu Thr
                        360
                                 365
Asp Ala Leu Phe Asp Leu Leu Ile Ala Leu Leu Lys Val Lys Arg Asn
                  375
Asp
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<210> 394
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Val Ser Leu Pro Leu Gln Ala Ala Ser Pro Val Lys Val Gly Ser Lys
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Ile Asp Thr Glu Gly Ala Leu Leu Gly Asn Ile Ile Leu Gln Val Leu
                     40
                                          45
Glu Ser His Gly Val Pro Thr Val Asn Lys Val Gln Leu Gly Thr Thr
                     55
Pro Val Val Arg Gly Ala Ile Thr Ser Gly Glu Leu Asp Ile Tyr Pro
                                    75
                  70
Glu Tyr Thr Gly Asn Gly Ala Phe Phe Phe Lys Asp Glu Asn Asp Ala
                               90
Ala Trp Lys Asn Ala Gln Gln Gly Tyr Glu Lys Val Lys Lys Leu Asp
                                             110
                             105
Ser Glu His Asn Lys Leu Ile Trp Leu Thr Pro Ala Pro Ala Asn Asn
           120
                                 125
      115
Thr Trp Thr Ile Ala Val Arg Gln Asp Val Ala Glu Lys Asn Lys Leu
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135
                                        140
Thr Ser Leu Ala Asp Leu Ser Arg Tyr Leu Gln Glu Gly Gly Thr Phe
                 150
                                     155
Lys Leu Ala Ala Ser Ala Glu Phe Ile Glu Arg Ala Asp Ala Leu Pro
              165
                                 170
Ala Phe Glu Lys Ala Tyr Gly Phe Lys Leu Gly Gln Asp Gln Leu Leu
                             185
Ser Leu Ala Gly Gly Asp Thr Ala Val Thr Ile Lys Ala Ala Ala Gln
                       200
      195
Gln Thr Ser Gly Val Asn Ala Ala Met Ala Tyr Gly Thr Asp Gly Pro
                                       220
           215
Val Ala Ala Leu Gly Leu Gln Thr Leu Ser Asp Pro Gln Gly Val Gln
                           235
                230
Pro Ile Tyr Ala Pro Ala Pro Val Val Arg Glu Ser Val Leu Arg Glu
                      250
              245
Tyr Pro Gln Met Ala Gln Trp Leu Gln Pro Val Phe Ala Ser Leu Asp
                                                 270
                             265
        260
Ala Lys Thr Leu Gln Gln Leu Asn Ala Ser Ile Ala Val Glu Gly Leu
                          280
Asp Ala Lys Lys Val Ala Ala Asp Tyr Leu Lys Gln Lys Gly Trp Thr
                      295
Lys
305
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Ser Gly Val Leu Leu Ala Gly Lys Leu Arg Met Asp Pro Phe Gly Val
Leu Val Leu Gly Val Val Thr Ala Val Gly Gly Gly Thr Ile Arg Asp
                          40
Met Ala Leu Asp His Gly Pro Val Phe Trp Val Lys Asp Pro Thr Asp
                       55
Leu Val Val Ala Met Val Thr Ser Met Leu Thr Ile Val Leu Val Arg
                  70
                                    75
Gln Pro Arg Arg Leu Pro Lys Trp Met Leu Pro Val Leu Asp Ala Val
                               90
              85
Gly Leu Ala Val Phe Val Gly Ile Gly Val Asn Lys Ala Phe Asn Ala
                             105
          100
Glu Ala Gly Pro Leu Ile Ala Val Cys Met Gly Val Ile Thr Gly Val
                                             125
                          120
    115
Gly Gly Gly Ile Ile Arg Asp Val Leu Ala Arg Glu Ile Pro Met Ile
                       135
                                         140
Leu Arg Thr Glu Ile Tyr Ala Thr Ala Cys Ile Ile Gly Gly Ile Val
                                     155
                  150
His Ala Thr Ala Tyr Tyr Thr Phe Ser Val Pro Leu Glu Thr Ala Ser
                                  170
               165
Met Met Gly Met Val Val Thr Leu Leu Ile Arg Leu Ala Ala Ile Arg
                              185
Trp His Leu Lys Leu Pro Thr Phe Ala Leu Asp Glu Asn Gly Arg
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<212> PRT

## <213> Escherichia coli

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<211> 232

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<213> Escherichia coli

<400> 397

Met Lys Ile Gly Ile Ile Gly Ala Met Glu Glu Glu Val Thr Leu Leu 10 1 Arg Asp Lys Ile Glu Asn Arg Gln Thr Ile Ser Leu Gly Gly Cys Glu 25 Ile Tyr Thr Gly Gln Leu Asn Gly Thr Glu Val Ala Leu Leu Lys Ser 40 Gly Ile Gly Lys Val Ala Ala Ala Leu Gly Ala Thr Leu Leu Glu-55 His Cys Lys Pro Asp Val Ile Ile Asn Thr Gly Ser Ala Gly Gly Leu 75 70 Ala Pro Thr Leu Lys Val Gly Asp Ile Val Val Ser Asp Glu Ala Arg 90 Tyr His Asp Ala Asp Val Thr Ala Phe Gly Tyr Glu Tyr Gly Gln Leu 105 Pro Gly Cys Pro Ala Gly Phe Lys Ala Asp Asp Lys Leu Ile Ala Ala

120

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Ala Glu Ala Cys Ile Ala Glu Leu Asn Leu Asn Ala Val Arg Gly Leu
                    135
                                140
Ile Val Ser Gly Asp Ala Phe Ile Asn Gly Ser Val Gly Leu Ala Lys
                   150
                                      155
Ile Arq His Asn Phe Pro Gln Ala Ile Ala Val Glu Met Glu Ala Thr
               165
                                  170
Ala Ile Ala His Val Cys His Asn Phe Asn Val Pro Phe Val Val Val
           180
                           185
Arg Ala Ile Ser Asp Val Ala Asp Gln Gln Ser His Leu Ser Phe Asp
                          200
Glu Phe Leu Ala Val Ala Ala Lys Gln Ser Ser Leu Met Val Glu Ser
Leu Val Gln Lys Leu Ala His Gly
                   230
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Met Ile Asp Lys Ser Ala Phe Val His Pro Thr Ala Ile Val Glu Glu
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Gly Ala Ser Ile Gly Ala Asn Ala His Ile Gly Pro Phe Cys Ile Val
                               25
Gly Pro His Val Glu Ile Gly Glu Gly Thr Val Leu Lys Ser His Val
                           40
Val Val Asn Gly His Thr Lys Ile Gly Arg Asp Asn Glu Ile Tyr Gln
                      55
Phe Ala Ser Ile Gly Glu Val Asn Gln Asp Leu Lys Tyr Ala Gly Glu
                   70
Pro Thr Arg Val Glu Ile Gly Asp Arg Asn Arg Ile Arg Glu Ser Val
Thr Ile His Arg Gly Thr Val Gln Gly Gly Gly Leu Thr Lys Val Gly
                              105
           100
Ser Asp Asn Leu Leu Met Ile Asn Ala His Ile Ala His Asp Cys Thr
       115
                        120
Val Gly Asn Arg Cys Ile Leu Ala Asn Asn Ala Thr Leu Ala Gly His
                      135
Val Ser Val Asp Asp Phe Ala Ile Ile Gly Gly Met Thr Ala Val His
                  150
                                      155
Gln Phe Cys Ile Ile Gly Ala His Val Met Val Gly Gly Cys Ser Gly
                                  170
              165
Val Ala Gln Asp Val Pro Pro Tyr Val Ile Ala Gln Gly Asn His Ala
                               185
Thr Pro Phe Gly Val Asn Ile Glu Gly Leu Lys Arg Arg Gly Phe Ser
                           200
Arg Glu Ala Ile Thr Ala Ile Arg Asn Ala Tyr Lys Leu Ile Tyr Arg
                                           220
                       215
Ser Gly Lys Thr Leu Asp Glu Val Lys Pro Glu Ile Ala Glu Leu Ala
                   230
                                      235
Glu Thr Tyr Pro Glu Val Lys Ala Phe Thr Asp Phe Phe Ala Arg Ser
Thr Arg Gly Leu Ile Arg
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<212> PRT
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Val Pro Asn Ala Arg Phe Val Gly Val Ala Gly Pro Arg Met Gln Ala
Glu Gly Cys Glu Ala Trp Tyr Glu Met Glu Glu Leu Ala Val Met Gly
                      55
Ile Val Glu Val Leu Gly Arg Leu Arg Arg Leu Leu His Ile Arg Ala
                                     75
                70
Asp Leu Thr Lys Arg Phe Gly Glu Leu Lys Pro Asp Val Phe Val Gly
                                  90
              85
Ile Asp Ala Pro Asp Phe Asn Ile Thr Leu Glu Gly Asn Leu Lys Lys
                            105
Gln Gly Ile Lys Thr Ile His Tyr Val Ser Pro Ser Val Trp Ala Trp
                                            125
                         120
Arg Gln Lys Arg Val Phe Lys Ile Gly Arg Ala Thr Asp Leu Val Leu
                                        140
                     135
Ala Phe Leu Pro Phe Glu Lys Ala Phe Tyr Asp Lys Tyr Asn Val Pro
                                     155
        150
Cys Arg Phe Ile Gly His Thr Met Ala Asp Ala Met Pro Leu Asp Pro
                                 170
              165
Asp Lys Asn Ala Ala Arg Asp Val Leu Gly Ile Pro His Asp Ala His
                           185
Cys Leu Ala Leu Leu Pro Gly Ser Arg Gly Ala Glu Val Glu Met Leu
                         200
Ser Ala Asp Phe Leu Lys Thr Ala Gln Leu Leu Arg Gln Thr Tyr Pro
                      215
                                         220
Asp Leu Glu Ile Val Val Pro Leu Val Asn Ala Lys Arg Arg Glu Gln
                230
                                   235
Phe Glu Arg Ile Lys Ala Glu Val Ala Pro Asp Leu Ser Val His Leu
             245
                                 250
Leu Asp Gly Met Gly Arg Glu Ala Met Val Ala Ser Asp Ala Ala Leu
                              265
Leu Ala Ser Gly Thr Ala Ala Leu Glu Cys Met Leu Ala Lys Cys Pro
                          280
Met Val Val Gly Tyr Arg Met Lys Pro Phe Thr Phe Trp Leu Ala Lys
                                          300
                       295
Arg Leu Val Lys Thr Asp Tyr Val Ser Leu Pro Asn Leu Leu Ala Gly
                                     315
                  310
Arg Glu Leu Val Lys Glu Leu Leu Gln Glu Glu Cys Glu Pro Gln Lys
               325
                                 330
Leu Ala Ala Ala Leu Leu Pro Leu Leu Ala Asn Gly Lys Thr Ser His
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Ala Met His Asp Thr Phe Arg Glu Leu His Gln Gln Ile Arg Cys Asn
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Ala Asp Glu Gln Ala Ala Gln Ala Val Leu Glu Leu Ala Gln
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Glu Val Gly Arg Gly Pro Leu Val Gly Ala Val Val Thr Ala Ala Val
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Arg	Ser	Glu	Glu	Glu 245	Met	Cys	Glu	Leu	Phe 250	Ala	Asp	Ile	Pro	Glu 255	Ala
Leu	Ala	Asn	Thr 260		Glu	Ile	Ala	Lys 265	_	Суз	Asn	Val	Thr 270	Val	Arg
Leu	Gly	Glu 275		Phe	Leu	Pro	Gln 280		Pro	Thr	Gly	Asp 285	Met	Ser	Thr
Glu	Asp 290		Leu	Val	Lys	Arg 295	Ala	Lys	Glu	Gly	Leu 300	Glu	Glu	Arg	Leu
305					Asp 310		•			315					320
_	_			325	Glu				330					335	
		-	340	•	Leu			345					350		
•		355			Val		360					365			
	370		_		Leu	375					380				
385					Arg 390					395					400
-		_		405	Phe				410					415	
			420		Tyr			425					430		
	_	435			Ala		440					445			
	450				Gly	455			-		460				
465	-				Thr 470					475					480
				485	Glu				490					495	
			500		Glu			505					510		
_	_	515			Ala		520					525			
_	530				Gly	535					540				
545			-		Gly 550					555					560
				565	Asn				570					575	
	_		580		Pro			585					590		
-	_	595					600					605			Val
	610				Arg	615					620				
625	_				Asp 630					635		•			640
_				645	Gly			•	650					655	
			660					665					670		Ser
	_	675					680					685			Glu
	690					695					700				Gly
Ala 705		Met	Leu	Arg	Arg 710	Ala	Met	Gly	Lys	Lys 715	Lys	Pro	Glu	Glu	Met 720

Ala Lys Gln Arg Ser Val Phe Ala Glu Gly Ala Glu Lys Asn Gly Ile 730 725 Asn Ala Glu Leu Ala Met Lys Ile Phe Asp Leu Val Glu Lys Phe Ala 745 Gly Tyr Gly Phe Asn Lys Ser His Ser Ala Ala Tyr Ala Leu Val Ser 760 Tyr Gln Thr Leu Trp Leu Lys Ala His Tyr Pro Ala Glu Phe Met Ala 775 780 Ala Val Met Thr Ala Asp Met Asp Asn Thr Glu Lys Val Val Gly Leu 785 790 795 Val Asp Glu Cys Trp Arg Met Gly Leu Lys Ile Leu Pro Pro Asp Ile 805 810 815 Asn Ser Gly Leu Tyr His Phe His Val Asn Asp Asp Gly Glu Ile Val 825 Tyr Gly Ile Gly Ala Ile Lys Gly Val Gly Glu Gly Pro Ile Glu Ala 835 840 Ile Ile Glu Ala Arg Asn Lys Gly Gly Tyr Phe Arg Glu Leu Phe Asp 855 860 Leu Cys Ala Arg Thr Asp Thr Lys Lys Leu Asn Arg Arg Val Leu Glu 870 875 Lys Leu Ile Met Ser Gly Ala Phe Asp Arg Leu Gly Pro His Arg Ala 890 Ala Leu Met Asn Ser Leu Gly Asp Ala Leu Lys Ala Ala Asp Gln His 905 910 Ala Lys Ala Glu Ala Ile Gly Gln Ala Asp Met Phe Gly Val Leu Ala 920 925 Glu Glu Pro Glu Gln Ile Glu Gln Ser Tyr Ala Ser Cys Gln Pro Trp 940 935 Pro Glu Gln Val Val Leu Asp Gly Glu Arg Glu Thr Leu Gly Leu Tyr 955 950 Leu Thr Gly His Pro Ile Asn Gln Tyr Leu Lys Glu Ile Glu Arg Tyr 970 Val Gly Gly Val Arg Leu Lys Asp Met His Pro Thr Glu Arg Gly Lys 985 980 Val Ile Thr Ala Ala Gly Leu Val Val Ala Ala Arg Val Met Val Thr 995 1000 Lys Arg Gly Asn Arg Ile Gly Ile Cys Thr Leu Asp Asp Arg Ser Gly 1010 1015 1020 Arg Leu Glu Val Met Leu Phe Thr Asp Ala Leu Asp Lys Tyr Gln Gln 1030 1035 1040 Leu Leu Glu Lys Asp Arg Ile Leu Ile Val Ser Gly Gln Val Ser Phe 1045 1050 Asp Asp Phe Ser Gly Gly Leu Lys Met Thr Ala Arg Glu Val Met Asp 1060 1065 1070 Ile Asp Glu Ala Arg Glu Lys Tyr Ala Arg Gly Leu Ala Ile Ser Leu 1080 1085 Thr Asp Arg Gln Ile Asp Asp Gln Leu Leu Asn Arg Leu Arg Gln Ser 1095 1100 1090 Leu Glu Pro His Arg Ser Gly Thr Ile Pro Val His Leu Tyr Tyr Gln 1105 1110 1115 Arg Ala Asp Ala Arg Ala Arg Leu Arg Phe Gly Ala Thr Trp Arg Val 1130 1135 1125 Ser Pro Ser Asp Arg Leu Leu Asn Asp Leu Arg Gly Leu Ile Gly Ser 1140 1145 Glu Gln Val Glu Leu Glu Phe Asp 1160 1155 <210> 402

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<400> 403

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Asp Arg His Gln Ile Arg Arg Val Leu His Glu Arg Leu Gly Tyr Glu
               165
                                  170
Gly Pro Glu Thr Pro Glu Ala Met Thr Leu Phe Ile Arg Gln Lys Ile
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Arg Glu Asp Phe Leu Ser Ala Glu Ile Gly Ile Thr Gly Cys Asn Phe
                          200
Ala Val Ala Glu Thr Gly Ser Val Cys Leu Val Thr Asn Glu Gly Asn
                      215
                                          220
Ala Arg Met Cys Thr Thr Leu Pro Lys Thr His Ile Ala Val Met Gly
                  230
                             235
Met Glu Arg Ile Ala Pro Thr Phe Ala Glu Val Asp Val Leu Ile Thr
                       250
Met Leu Ala Arg Ser Ala Val Gly Ala Arg Leu Thr Gly Tyr Asn Thr
                               265
Trp Leu Thr Gly Pro Arg Glu Ala Gly His Val Asp Gly Pro Glu Glu
                                              285
Phe His Leu Val Ile Val Asp Asn Gly Arg Ser Glu Val Leu Ala Ser
                       295
                                          300
Glu Phe Arg Asp Val Leu Arg Cys Ile Arg Cys Gly Ala Cys Met Asn
                                       315
                  310
Thr Cys Pro Ala Tyr Arg His Ile Gly Gly His Gly Tyr Gly Ser Ile
Tyr Pro Gly Pro Ile Gly Ala Val Ile Ser Pro Leu Leu Gly Gly Tyr
                              345
Lys Asp Phe Lys Asp Leu Pro Tyr Ala Cys Ser Leu Cys Thr Ala Cys
               360
Asp Asn Val Cys Pro Val Arg Ile Pro Leu Ser Lys Leu Ile Leu Arg
                       375
                                          380
His Arg Arg Val Met Ala Glu Lys Gly Ile Thr Ala Lys Ala Glu Gln
                                       395
                   390
Arg Ala Ile Lys Met Phe Ala Tyr Ala Asn Ser His Pro Gly Leu Trp
               405
                                   410
Lys Val Gly Met Met Ala Gly Ala His Ala Ala Ser Trp Phe Ile Asn
           420
                              425
Gly Gly Lys Thr Pro Leu Lys Phe Gly Ala Ile Ser Asp Trp Met Glu
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Ala Arg Asp Leu Pro Glu Ala Asp Gly Glu Ser Phe Arg Ser Trp Phe
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Lys Lys His Gln Ala Gln Glu Lys Lys Asn Gly
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Asn Leu Ala Arg Leu Ala Thr Gly Trp Lys His Ala Ile Phe Leu Lys
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                           40
Arg Lys Arg Met Asp Asn Arg Gly Glu Phe Leu Asn Asn Val Ala Gln
                       55
                                          60
Ala Leu Gly Arg Pro Leu Arg Leu Glu Pro Gln Ala Glu Asp Ala Pro
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                                       75
Leu Asn Asn Tyr Ala Asn Glu Arg Leu Thr Gln Leu Asn Gln Gln
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Arg Cys Asp Ala Phe Ile Gln Phe Ala Ser Asp Val Met Leu Thr Arg
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110
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Cys Glu Leu Thr Ser Glu Ala Lys Ala Ala Glu Ala Ala Ile Arg Leu
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               120
Cys Lys Glu Leu Gly Asp Gln Ser Val Val Ile Ser Gly Asp Thr Arq
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          135
Leu Glu Glu Leu Gly Ile Ser Glu Arg Leu Gln Gln Glu Cys Asn Ala
                150
                                   155
Val Val Trp Asp Pro Ala Lys Gly Ala Glu Asn Ile Ser Gln Ala Glu
                               170
Gln Ala Lys Val Gly Val Val Tyr Ala Glu Tyr Gly Leu Thr Glu Ser
                           185
Gly Gly Val Val Leu Phe Ser Ala Ala Glu Arg Gly Arg Ser Leu Ser
                       200
       195
Leu Leu Pro Glu Tyr Ser Leu Phe Ile Leu Arg Lys Ser Thr Ile Leu
                    215
                                      220
Pro Arg Val Ala Gln Leu Ala Glu Lys Leu His Gln Lys Ala Gln Ala
                                  235
               230
Gly Glu Arg Met Pro Ser Cys Ile Asn Ile Ile Ser Gly Pro Ser Ser
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Lys Ala Val Tyr Leu Ile Ile Glu Asp Cys
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Phe Thr His Glu Lys Trp Met Asp Asp Ser Thr Leu Lys Glu Phe Ile
                      40
Lys Gln Tyr Ile Ala Ala Ser Gly Asn Gln Val Tyr Phe Thr Trp Gln
                                      60
                    55
Gly Gly Glu Pro Thr Leu Ala Gly Leu Asp Phe Phe Arg Lys Val Ile
                                   75
                  70
His Tyr Gln Gln Arg Tyr Ala Gly Gln Lys Arg Ile Phe Asn Ala Leu
                               90
             85
Gln Thr Asn Gly Ile Leu Leu Asn Asn Glu Trp Cys Ala Phe Leu Lys
          100
                            105
Glu His Glu Phe Leu Val Gly Ile Ser Ile Asp Gly Pro Gln Glu Leu
                        120
                                          125
His Asp Arg Tyr Arg Arg Ser Asn Ser Gly Asn Gly Thr Phe Ala Lys
                                      140
                    135
Val Ile Ala Ala Ile Glu Arg Leu Lys Ser Tyr Gln Val Glu Phe Asn
                                   155
                 150
Thr Leu 'Thr Val Ile Asn Asn Val Asn Val His Tyr Pro Leu Glu Val
            165
                                170
Tyr His Phe Leu Lys Ser Ile Gly Ser Lys His Met Gln Phe Ile Glu
                            185
                                    190
          180
Leu Leu Glu Thr Gly Thr Pro Asn Ile Asp Phe Ser Gly His Ser Glu
                        200 205
Asn Thr Phe Arg Ile Ile Asp Phe Ser Val Pro Pro Thr Ala Tyr Gly
 210 215
                                      220
Lys Phe Met Ser Thr Ile Phe Met Gln Trp Val Lys Asn Asp Val Gly
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                  230
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Glu Ile Phe Ile Arg Gln Phe Glu Ser Phe Val Ser Arg Phe Leu Gly
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Asn Gly His Thr Ser Cys Ile Phe Gln Glu Ser Cys Lys Asp Asn Leu
           260
                             265
Val Val Glu Ser Asn Gly Asp Ile Tyr Glu Cys Asp His Phe Val Tyr
                          280
Pro Gln Tyr Lys Ile Gly Asn Ile Asn Lys Ser Glu Leu Lys Thr Met
                     295
Asn Ser Val Gln Leu Thr Ala Gln Lys Lys Arg Ile Pro Ala Lys Cys
                  310 315
Gln Gln Cys Ala Tyr Lys Pro Ile Cys Asn Gly Gly Cys Pro Lys His
            325
                                330
Arg Ile Thr Lys Val Asn Asn Glu Thr Val Ser Tyr Phe Cys Glu Gly
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                              345
Tyr Lys Ile Leu Phe Ser Thr Met Val Pro Tyr Met Asn Ala Met Val
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Glu Leu Ala Lys Asn Arg Val Pro Leu Tyr His Ile Met Asp Val Ala
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Lys Gln Met Glu Asn Asn
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Lys Lys Ser Val Val Ser Thr Ser Ile Ser Leu Ile Leu Ala Ser Gly
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Met Ala Ala Phe Ala Ala His Ala Ala Asp Asp Val Lys Leu Lys Ala
                          40
Thr Lys Thr Asn Val Ala Phe Ser Asp Phe Thr Pro Thr Glu Tyr Ser
                      55
Thr Lys Gly Lys Pro Asn Ile Ile Val Leu Thr Met Asp Asp Leu Gly
                  70
                          75
Tyr Gly Gln Leu Pro Phe Asp Lys Gly Ser Phe Asp Pro Lys Thr Met
             85
                                  90
Glu Asn Arg Glu Val Val Asp Thr Tyr Lys Ile Gly Ile Asp Lys Ala
                            105
Ile Glu Ala Ala Gln Lys Ser Thr Pro Thr Leu Leu Ser Leu Met Asp
                          120
Glu Gly Val Arg Phe Thr Asn Gly Tyr Val Ala His Gly Val Ser Gly
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                                          140
Pro Ser Arg Ala Ala Ile Met Thr Gly Arg Ala Pro Ala Arg Phe Gly
                                     155
                  150
Val Tyr Ser Asn Thr Asp Ala Gln Asp Gly Ile Pro Leu Thr Glu Thr
                                  170
Phe Leu Pro Glu Leu Phe Gln Asn His Gly Tyr Tyr Thr Ala Ala Val
                              185
Gly Lys Trp His Leu Ser Lys Ile Ser Asn Val Pro Val Pro Glu Asp
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                          200
                                             205
Lys Gln Thr Arg Asp Tyr His Asp Asn Phe Thr Thr Phe Ser Ala Glu
                      215
                                         220
Glu Trp Gln Pro Gln Asn Arg Gly Phe Asp Tyr Phe Met Gly Phe His
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Ala Ala Gly Thr Ala Tyr Tyr Asn Ser Pro Ser Leu Phe Lys Asn Arg
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Glu Arg Val Pro Ala Lys Gly Tyr Ile Ser Asp Gln Leu Thr Asp Glu
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265

260

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Ala Ile Gly Val Val Asp Arg Ala Lys Thr Leu Asp Gln Pro Phe Met
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Leu Tyr Leu Ala Tyr Asn Ala Pro His Leu Pro Asn Asp Asn Pro Ala
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Pro Asp Gln Tyr Gln Lys Gln Phe Asn Thr Gly Ser Gln Thr Ala Asp
                                    315
               310
Asn Tyr Tyr Ala Ser Val Tyr Ser Val Asp Gln Gly Val Lys Arg Ile
                                 330
              325
Leu Glu Gln Leu Lys Lys Asn Gly Gln Tyr Asp Asn Thr Ile Ile Leu
                            345
Phe Thr Ser Asp Asn Gly Ala Val Ile Asp Gly Pro Leu Pro Leu Asn
                360
Gly Ala Gln Lys Gly Tyr Lys Ser Gln Thr Tyr Pro Gly Gly Thr His
                                         380
             375
Thr Pro Met Phe Met Trp Trp Lys Gly Lys Leu Gln Pro Gly Asn Tyr
                                     395
       390
Asp Lys Leu Ile Ser Ala Met Asp Phe Tyr Pro Thr Ala Leu Asp Ala
                                 410
Ala Asp Ile Ser Ile Pro Lys Asp Leu Lys Leu Asp Gly Val Ser Leu
                              425
           420
Leu Pro Trp Leu Gln Asp Lys Lys Gln Gly Glu Pro His Lys Asn Leu
                                            445
      435
                         440
Thr Trp Ile Thr Ser Tyr Ser His Trp Phe Asp Glu Glu Asn Ile Pro
                      455
                                         460
Phe Trp Asp Asn Tyr His Lys Phe Val Arg His Gln Ser Asp Asp Tyr
                                     475
                470
Pro His Asn Pro Asn Thr Glu Asp Leu Ser Gln Phe Ser Tyr Thr Val
                                 490
              485
Arg Asn Asn Asp Tyr Ser Leu Val Tyr Thr Val Glu Asn Asn Gln Leu
                              505
Gly Leu Tyr Lys Leu Thr Asp Leu Gln Gln Lys Asp Asn Leu Ala Ala
                          520
Ala Asn Pro Gln Val Val Lys Glu Met Gln Gly Val Val Arg Glu Phe
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Ile Asp Ser Ser Gln Pro Pro Leu Ser Glu Val Asn Gln Glu Lys Phe
545 550
Asn Asn Ile Lys Lys Ala Leu Ser Glu Ala Lys
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           20
His Ser Lys Thr Met Met Ala Ala Phe Ile Ile Ala Ile Lys Gly Thr
                          40
        35
Ile Lys Gln Ala Val Met Leu Gly Leu Ala Ala Thr Ile Ser His Thr
                       55
Ala Val Val Trp Leu Ile Ala Phe Gly Gly Met Val Ile Ser Lys Arg
                                     75
                   70
Phe Thr Ala Gln Ser Ala Glu Pro Trp Leu Gln Leu Ile Ser Ala Val
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Ile Ile Ile Ser Thr Ala Phe Trp Met Phe Trp Arg Thr Trp Arg Gly
                              105
           100
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Glu Arg Asn Trp Leu Glu Asn Met His Gly His Asp Tyr Glu His His
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His His Asp His Glu His His His Asp His Gly His His His His
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Glu His Gly Glu Tyr Gln Asp Ala His Ala Arg Ala His Ala Asn Asp
                         155
                  150
Ile Lys Arg Arg Phe Asp Gly Arg Glu Val Thr Asn Trp Gln Ile Leu
                                170
              165
Leu Phe Gly Leu Thr Gly Gly Leu Ile Pro Cys Pro Ala Ala Ile Thr
                             185
Val Leu Leu Ile Cys Ile Gln Leu Lys Ala Leu Thr Leu Gly Ala Thr
                         200
Leu Val Val Ser Phe Ser Ile Gly Leu Ala Leu Thr Leu Val Thr Val
           215
                                         220
Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser
          230
                                   235
Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu
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Ile Gly Leu Val Gly Val Tyr Met Gly Val His Gly Phe Met Gly Ile
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Met Arg
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Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg Tyr
    35
                         40
Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile Lys
                      55
Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala Trp
                70 75
Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser Lys
                                90
              85
Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro Gly
                             105
Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys Gln
                          120
Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp Thr
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                                        140
Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys Ile
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Thr	Lys 50		Asn	Cys	Tyr	Glu 55	Cys	Ser	Met	Lys	Leu 60	Asp	Tyr	Ile	Lys
Gln 65		Tyr	Phe	Ser	Leu 70	Glu	Thr	Ala	Trp	Tyr 75	Leu	Ile	Ser	Ala	Val 80
	Val	Phe	Ile	Ala 85	Ser	Val	Phe	Ile	Gln 90	His	Arg	Ile	Lys	Ala 95	Tyr
Leu	Thr	Leu	Leu 100	Ala	Ile	Thr	Trp	Ile 105	Val	Leu	Thr	Ile	Thr 110	Asp	Val
Ala	Leu	Ile 115		Ala	Leu	Asp	Asn 120	Ile	Ala	Met	Asn	Asn 125	Ile	Leu	Leu
Asn	Ile 130		Tyr	Asn	Leu	Phe 135	Gly	Ala	Ile	Leu	Leu 140	Ser	Leu	Phe	Met
Cvs		Ser	Asn	Ser	Leu	Leu	Phe	His	Leu	Asn	Lys	Ile	Lys	His	Ile
145					150					155	_		_		160
	Met	Ile	Leu	Ser 165			Ile	Pro	Leu 170	Val	Ser	Ala	Ile	Ile 175	Ile
Ala	Ile	Leu	Ile 180	Thr	Ala	Val	Ile	Tyr 185	Leu	Leu	Phe	Ala	Arg 190	Gln	Ala
Val	Glu	Ile 195	Glu	Met	Asp	Ile	Ser 200	Glu	Gly	Ser	Asp	Ile 205	Ala	Tyr	Val
Gly	Val 210	Lys	Asp	Asn	Glu	Glu 215	Ser	Phe	Gly	Phe	Leu 220	Asn	Asp	Lys	Lys
Thr 225	Asp	Thr	Pro	Thr	Tyr 230	Leu	Asp	Val	Ile	Lys 235	Asn	Gly	Ser	Leu	11e 240
Tyr	Asn	Asp	Thr	Gln 245	Gly	Leu	Ser	Gly	Ala 250	Asp	Ile	Tyr	Ile	Val 255	Ser
Gly	Суз	Tyr	Ala 260	Leu	Pro	Asp	Leu	Leu 265	Arg	Asn	Val	Pro	Leu 270	Asp	Ala
Lys	Lys	Ser 275	Phe	Leu	Asn	Val	Lys 280	Lys	Leu	Glu	Ile	Thr 285	Gln	Lys	Leu
Pro	Met 290	Met	Gly	Phe	Ile	Gln 295	Gly	Glu	Ser	Ala	Asp 300	Val	Met	Pro	Lys
Ala 305	Ala	Ser	Arg	Leu	Ser 310	Leu	Ser	Lys	Gln	Asp 315	Asp	Lys	Phe	Met	Leu 320
Ala	Ser	Ser	Val	Thr 325	Asp	Ser	Gln	Ile	Lys 330	Phe	Lys	Ser	Asn	Asn 335	Ala
			340				Phe	345				,	350		
Leu	His	Asp 355					11e 360		Ile			Lys 365		Tyr	Lys
	370					375			_		380				Lys
Met	Lys	Cys	Glu	Tyr	Gln	Gln	Ile	Ser	Asp	Leu	Thr	Asn	Thr	Tyr	Asn
385					390				*	395					400
				405					410					415	Asp
Asp	Ile	Ile	Asn 420	Tyr	Asn	Asn	Ser	Pro 425	Ser	Val	Leu	Leu	Lys 430	Thr	Asp
Phe	Ala	Phe 435	Tyr	Lys	Lys	Thr	Tyr 440	Gln	Lys	Leu	Asp	Lys 445	Ile	Tyr	Asp
Asp	Ile 450	Ser	Asn	Gly	Lys	Leu 455	Ser	Ser	Leu	Arg	Ala 460	Thr	Gly	Ile	Ser
Gln 465	Phe	Ser	Ile	Asn	Gly 470	Lys	His	Leu	Ser	Leu 475	Arg	Pro	Glu	Ser	Glu 480
Ile	Ile	Ile	Ser	Glu 485	Gly	Ser	Leu	Tyr	Gly 490		Val	Asn	Lys	Ser 495	Lys

Lys Ile Lys Ile Tyr Gly Thr Ala Asp Leu Val Phe Val Asp Asn Lys 500 505 Ile Met Asn Leu Arg Lys Ile Thr Tyr Leu Gln Ser Lys Leu Glu Ile 520 525 Phe Gly Ser Ser Ile Met Asp Ile Leu Lys Tyr Ile Phe Gly Leu Gly 535 Leu Leu Ala Ile Ser Ile Lys Phe Ile His Ser Tyr Phe Lys Asn Asp 550 555 Val Asn Glu Asn Leu Phe Leu 565 <210> 410 <211> 363 <212> PRT <213> Escherichia coli <400> 410 Met Ser Asn Phe Ile Asn Ile His Val Leu Ile Ser His Ser Pro Ser 10 Cys Leu Asn Arg Asp Asp Met Asn Met Gln Lys Asp Ala Ile Phe Gly 25 Gly Lys Arg Arg Val Arg Ile Ser Ser Gln Ser Leu Lys Arg Ala Met 40 45 Arg Lys Ser Gly Tyr Tyr Ala Gln Asn Ile Gly Glu Ser Ser Leu Arg 55 50 Thr Ile His Leu Ala Gln Leu Arg Asp Val Leu Arg Gln Lys Leu Gly 70 75 Glu Arg Phe Asp Gln Lys Ile Ile Asp Lys Thr Leu Ala Leu Leu Ser 90 85 Gly Lys Ser Val Asp Glu Ala Glu Lys Ile Ser Ala Asp Ala Val Thr 100 105 Pro Trp Val Val Gly Glu Ile Ala Trp Phe Cys Glu Gln Val Ala Lys 120 Ala Glu Ala Asp Asn Leu Asp Asp Lys Lys Leu Leu Lys Val Leu Lys 135 140 Glu Asp Ile Ala Ala Ile Arg Val Asn Leu Gln Gln Gly Val Asp Ile 150 155 Ala Leu Ser Gly Arg Met Ala Thr Ser Gly Met Met Thr Glu Leu Gly 165 170 Lys Val Asp Gly Ala Met Ser Ile Ala His Ala Ile Thr Thr His Gln 185 Val Asp Ser Asp Ile Asp Trp Phe Thr Ala Val Asp Asp Leu Gln Glu 200 Gln Gly Ser Ala His Leu Gly Thr Gln Glu Phe Ser Ser Gly Val Phe 215 220 Tyr Arg Tyr Ala Asn Ile Asn Leu Ala Gln Leu Gln Glu Asn Leu Gly 230 235 Gly Ala Ser Arg Glu Gln Ala Leu Glu Ile Ala Thr His Val Val His 250 245 Met Leu Ala Thr Glu Val Pro Gly Ala Lys Gln Arg Thr Tyr Ala Ala 260 265 Phe Asn Pro Ala Asp Met Val Met Val Asn Phe Ser Asp Met Pro Leu 280 Ser Met Ala Asn Ala Phe Glu Lys Ala Val Lys Ala Lys Asp Gly Phe 300 Leu Gln Pro Ser Ile Gln Ala Phe Asn Gln Tyr Trp Asp Arg Val Ala 310 315 Asn Gly Tyr Gly Leu Asn Gly Ala Ala Ala Gln Phe Ser Leu Ser Asp 325 330 335 Val Asp Pro Ile Thr Ala Gln Val Lys Gln Met Pro Thr Leu Glu Gln

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Thr Gly Trp Ile Ile Asp Phe Ala Glu Leu Lys Ala Ala Phe Lys Pro
Thr Tyr Glu Arg Leu Asp His His Tyr Leu Asn Asp Ile Pro Gly Leu
                70
                                 75
Glu Asn Pro Thr Ser Glu Val Leu Ala Lys Trp Ile Trp Asp Gln Val
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Thr Ala Gly Cys Ile Tyr Arg Gly Glu
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Pro Gly Ser Lys Asn Leu Ser Gly Gly Arg Leu Tyr Thr His Ala Leu
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                     55
Ala Glu Leu Leu Pro Gln Phe His Leu Thr Ala Pro Leu Glu Arg Arg
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                             75
Ile Thr His Glu Ser Leu Ser Leu Leu Thr Pro Asp Gly Val Thr Thr
Phe Ser Ser Leu Gln Pro Gly Gly Glu Ser Trp Ser Val Leu Arg Ala
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          100
Arg Phe Asp Pro Trp Leu Val Ala Glu Ala Glu Lys Glu Gly Val Glu
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                                            125
Cys Ile Pro Gly Ala Thr Val Asp Ala Leu Tyr Glu Glu Asn Gly Arg
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                     135
Val Cys Gly Val Ile Cys Gly Asp Asp Ile Leu Arg Ala Arg Tyr Val
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                                    155
Val Leu Ala Glu Gly Ala Asn Ser Val Leu Ala Glu Arg His Gly Leu
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              165
Val Thr Arg Pro Ala Gly Glu Ala Met Ala Leu Gly Ile Lys Glu Val
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Leu Ser Leu Glu Thr Ser Ala Ile Glu Glu Arg Phe His Leu Glu Asn
               200 205
Asn Glu Gly Ala Ala Leu Leu Phe Ser Gly Arg Ile Cys Asp Asp Leu
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Pro Gly Gly Ala Phe Leu Tyr Thr Asn Gln Gln Thr Leu Ser Leu Gly
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Ile Val Cys Pro Leu Ser Ser Leu Thr Gln Ser Arg Val Pro Ala Ser
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Glu Leu Leu Thr Arg Phe Lys Ala His Pro Ala Val Arg Pro Leu Ile
          260
                              265
Lys Asn Thr Glu Ser Leu Glu Tyr Gly Ala His Leu Val Pro Glu Gly
                          280
Gly Leu His Ser Met Pro Val Gln Tyr Ala Gly Asn Gly Trp Leu Leu
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                                         300
Val Gly Asp Ala Leu Arg Ser Cys Val Asn Thr Gly Ile Ser Val Arg
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                  310
Gly Met Asp Met Ala Leu Thr Gly Ala Gln Ala Ala Gln Thr Leu
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                                   330
Ile Ser Ala Cys Gln His Arg Glu Pro Gln Asn Leu Phe Pro Leu Tyr
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           340
His His Asn Val Glu Arg Ser Leu Leu Trp Asp Val Leu Gln Arg Tyr
                           360
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Gln His Val Pro Ala Leu Leu Gln Arg Pro Gly Trp Tyr Arg Thr Trp
                      375
                                          380
Pro Ala Leu Met Gln Asp Ile Ser Arg Asp Leu Trp Asp Gln Gly Asp
                   390
                                      395
Lys Pro Val Pro Pro Leu Arg Gln Leu Phe Trp His His Leu Arg Arg
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His Gly Leu Trp His Leu Ala Gly Asp Val Ile Arg Ser Leu Arg Cys
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Ser Val Glu Arg Gln Thr Ala Glu Arg Leu Ile Asn Ala Cys Pro Ala
                          40
Gly Leu Phe Ser Leu Thr Pro Glu Gly Asn Leu Arg Ile Asp Tyr. Arg
Ser Cys Leu Glu Cys Gly Thr Cys Arg Leu Leu Cys Asp Glu Ser Thr
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Phe Gly
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Met Pro Leu Leu His Leu Leu Arg Gln Asn Pro Val Ile Ala Ala Val
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10

Lys Asp Asn Ala Ser Leu Gln Leu Ala Ile Asp Ser Glu Cys Gln Phe

5

1

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30
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                           25
Ile Ser Val Leu Tyr Gly Asn Ile Cys Thr Ile Ser Asn Ile Val Lys
                               45
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Lys Ile Lys Asn Ala Gly Lys Tyr Ala Phe Ile His Val Asp Leu Leu
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Glu Gly Ala Ser Asn Lys Glu Val Val Ile Gln Phe Leu Lys Leu Val
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Thr Glu Ala Asp Gly Ile Ile Ser Thr Lys Ala Ser Met Leu Lys Ala
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            85
Ala Arg Ala Glu Gly Phe Phe Cys Ile His Arg Leu Phe Ile Val Asp
                          105 110
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Ser Ile Ser Phe His Asn Ile Asp Lys Gln Val Ala Gln Ser Asn Pro
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Asp Cys Ile Glu Ile Leu Pro Gly Cys Met Pro Lys Val Leu Gly Trp
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                                    140
Val Thr Glu Lys Ile Arg Gln Pro Leu Ile Ala Gly Gly Leu Val Cys
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Asp Glu Glu Asp Ala Arg Asn Ala Ile Asn Ala Gly Val Val Ala Leu
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Gln Gln Ala Leu Gln Tyr Glu Leu Glu Lys Asn Lys Ala Glu Leu Asp
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Glu Tyr Arg Glu Glu Leu Val Ser His Phe Ala Arg Ser Ala Glu Leu
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Leu Asp Thr Met Ala His Asp Tyr Arg Gln Leu Tyr Gln His Met Ala
                 70
                                  75
Lys Ser Ser Ser Leu Leu Pro Glu Leu Ser Ala Glu Ala Asn Pro
                              90
            85
Phe Arg Asn Arg Leu Ala Glu Ser Glu Ala Ser Asn Asp Gln Ala Pro
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Val Gln Met Pro Arg Asp Tyr Ser Glu Gly Ala Ser Gly Leu Leu Arg
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Thr Gly Ala Lys Arg Asp
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Leu Thr Leu Ser Ala Ser Phe Gln Ala Val Ala Ser Ile Pro Gly Gln
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Val Ala Asp Gln Ala Pro Leu Pro Ser Leu Ala Pro Met Leu Glu Lys
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Val Leu Pro Ala Val Val Ser Val Arg Val Glu Gly Thr Ala Ser Gln
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55
Gly Gln Lys Ile Pro Glu Glu Phe Lys Lys Phe Phe Gly Asp Asp Leu
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Pro Asp Gln Pro Ala Gln Pro Phe Glu Gly Leu Gly Ser Gly Val Ile
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Ile Asn Ala Ser Lys Gly Tyr Val Leu Thr Asn Asn His Val Ile Asn
                            105
         100
Gln Ala Gln Lys Ile Ser Ile Gln Leu Asn Asp Gly Arg Glu Phe Asp
                 120
Ala Lys Leu Ile Gly Ser Asp Asp Gln Ser Asp Ile Ala Leu Leu Gln
           135
                                      140
Ile Gln Asn Pro Ser Lys Leu Thr Gln Ile Ala Ile Ala Asp Ser Asp
       150
                                  155
Lys Leu Arg Val Gly Asp Phe Ala Val Ala Val Gly Asn Pro Phe Gly
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            165
Leu Gly Gln Thr Ala Thr Ser Gly Ile Val Ser Ala Leu Gly Arg Ser
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Gly Leu Asn Leu Glu Gly Leu Glu Asn Phe Ile Gln Thr Asp Ala Ser
                        200
Ile Asn Arg Gly Asn Ser Gly Gly Ala Leu Leu Asn Leu Asn Gly Glu
                    215
Leu Ile Gly Ile Asn Thr Ala Ile Leu Ala Pro Gly Gly Gly Ser Val
                                   235
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Gly Ile Gly Phe Ala Ile Pro Ser Asn Met Ala Arg Thr Leu Ala Gln
                               250
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Gln Leu Ile Asp Phe Gly Glu Ile Lys Arg Gly Leu Leu Gly Ile Lys
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Gly Thr Glu Met Ser Ala Asp Ile Ala Lys Ala Phe Asn Leu Asp Val
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Gln Arg Gly Ala Phe Val Ser Glu Val Leu Pro Gly Ser Gly Ser Ala
           295 300
Lys Ala Gly Val Lys Ala Gly Asp Ile Ile Thr Ser Leu Asn Gly Lys
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                                315
Pro Leu Asn Ser Phe Ala Glu Leu Arg Ser Arg Ile Ala Thr Thr Glu
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Pro Gly Thr Lys Val Lys Leu Gly Leu Leu Arg Asn Gly Lys Pro Leu
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Glu Val Glu Val Thr Leu Asp Thr Ser Thr Ser Ser Ser Ala Ser Ala
       355 360 365
Glu Met Ile Thr Pro Ala Leu Glu Gly Ala Thr Leu Ser Asp Gly Gln
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Leu Lys Asp Gly Gly Lys Gly Ile Lys Ile Asp Glu Val Val Lys Gly
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                                    395
Ser Pro Ala Ala Gln Ala Gly Leu Gln Lys Asp Asp Val Ile Ile Gly
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                               410 415
Val Asn Arg Asp Arg Val Asn Ser Ile Ala Glu Met Arg Lys Val Leu
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Ser Ile Tyr Leu Leu Met Arg
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Leu Ala Val Arg Arg Ala Ala Pro Ala Val Val Asn Val Tyr Asn Arg
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Gly Leu Asn Thr Asn Ser His Asn Gln Leu Glu Ile Arg Thr Leu Gly
Ser Gly Val Ile Met Asp Gln Arg Gly Tyr Ile Ile Thr Asn Lys His
                                  90
Val Ile Asn Asp Ala Asp Gln Ile Ile Val Ala Leu Gln Asp Gly Arg
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Val Phe Glu Ala Leu Leu Val Gly Ser Asp Ser Leu Thr Asp Leu Ala
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                          120
Val Leu Lys Ile Asn Ala Thr Gly Gly Leu Pro Thr Ile Pro Ile Asn
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Ala Arg Arg Val Pro His Ile Gly Asp Val Val Leu Ala Ile Gly Asn
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Pro Tyr Asn Leu Gly Gln Thr Ile Thr Gln Gly Ile Ile Ser Ala Thr
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Gly Arg Ile Gly Leu Asn Pro Thr Gly Arg Gln Asn Phe Leu Gln Thr
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Asp Ala Ser Ile Asn His Gly Asn Ser Gly Gly Ala Leu Val Asn Ser
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Leu Gly Glu Leu Met Gly Ile Asn Thr Leu Ser Phe Asp Lys Ser Asn
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Asp Gly Glu Thr Pro Glu Gly Ile Gly Phe Ala Ile Pro Phe Gln Leu
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                  230
Ala Thr Lys Ile Met Asp Lys Leu Ile Arg Asp Gly Arg Val Ile Arg
              245
                                  250
Gly Tyr Ile Gly Ile Gly Gly Arg Glu Ile Ala Pro Leu His Ala Gln
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Gly Gly Gly Ile Asp Gln Leu Gln Gly Ile Val Val Asn Glu Val Ser
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Pro Asp Gly Pro Ala Ala Asn Ala Gly Ile Gln Val Asn Asp Leu Ile
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                                          300
Ile Ser Val Asp Asn Lys Pro Ala Ile Ser Ala Leu Glu Thr Met Asp
                                      315
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Gln Val Ala Glu Ile Arg Pro Gly Ser Val Ile Pro Val Val Wet
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Arg Asp Asp Lys Gln Leu Thr Leu Gln Val Thr Ile Gln Glu Tyr Pro
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Ala Thr Asn
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 Ile Ala Leu Thr Ser Ile Tyr Gly Val Gly Lys Thr Arg Ser Lys Ala
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 Ile Leu Ala Ala Gly Ile Ala Glu Asp Val Lys Ile Ser Glu Leu
                           40
 Ser Glu Gly Gln Ile Asp Thr Leu Arg Asp Glu Val Ala Lys Phe Val
                       55
 Val Glu Gly Asp Leu Arg Arg Glu Ile Ser Met Ser Ile Lys Arg Leu
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Lys Met Glu Gly Thr Phe Lys Arg Lys Pro Glu Arg Ser Asp Leu Ser
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Ala Asp Ile Asn Glu His Leu Ile Val Glu Leu Tyr Ser Lys
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Arg Gly Phe Gly His Thr Leu Gly Asn Ala Leu Arg Arg Ile Leu Leu
                                          45
                        40
Ser Ser Met Pro Gly Cys Ala Val Thr Glu Val Glu Ile Asp Gly Val
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Leu His Glu Tyr Ser Thr Lys Glu Gly Val Gln Glu Asp Ile Leu Glu
Ile Leu Leu Asn Leu Lys Gly Leu Ala Val Arg Val Gln Gly Lys Asp
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Glu Val Ile Leu Thr Leu Asn Lys Ser Gly Ile Gly Pro Val Thr Ala
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Ala Asp Ile Thr His Asp Gly Asp Val Glu Ile Val Lys Pro Gln His
                      120
Val Ile Cys His Leu Thr Asp Glu Asn Ala Ser Ile Ser Met Arg Ile
                    135
                               140
Lys Val Gln Arg Gly Arg Gly Tyr Val Pro Ala Ser Thr Arg Ile His
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Ser Glu Glu Asp Glu Arg Pro Ile Gly Arg Leu Leu Val Asp Ala Cys
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Tyr Ser Pro Val Glu Arg Ile Ala Tyr Asn Val Glu Ala Ala Arg Val
       180 . 185
Glu Gln Arg Thr Asp Leu Asp Lys Leu Val Ile Glu Met Glu Thr Asn
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Gly Thr Ile Asp Pro Glu Glu Ala Ile Arg Arg Ala Ala Thr Ile Leu
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                     215
Ala Glu Gln Leu Glu Ala Phe Val Asp Leu Arg Asp Val Arg Gln Pro
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                230
Glu Val Lys Glu Glu Lys Pro Glu Phe Asp Pro Ile Leu Leu Arg Pro
             245
                               250
Val Asp Asp Leu Glu Leu Thr Val Arg Ser Ala Asn Cys Leu Lys Ala
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Glu Ala Ile His Tyr Ile Gly Asp Leu Val Gln Arg Thr Glu Val Glu
                                         285
      275 . 280
Leu Leu Lys Thr Pro Asn Leu Gly Lys Lys Ser Leu Thr Glu Ile Lys
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Asp. Val Leu Ala Ser Arg Gly Leu Ser Leu Gly Met Arg Leu Glu Asn
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Trp Pro Pro Ala Ser Ile Ala Asp Glu
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Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val
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Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg
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Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe
                   70
Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg
                                  90
Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr
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Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu
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<211> 46
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Met Lys Arg Thr Phe Gln Pro Ser Val Leu Lys Arg Asn Arg Ser His
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Arg Arg Arg Ala Lys Gly Arg Ala Arg Leu Thr Val Ser Lys
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Gln Phe Thr Phe Val Phe Gln Gln Pro Gln Arg Ala Gly Thr Pro Gln
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Ile Thr Ile Leu Gly Arg Leu Asn Ser Leu Gly His Pro Arg Ile Gly
Leu Thr Val Ala Lys Lys Asn Val Arg Arg Ala His Glu Arg Asn Arg
Ile Lys Arg Leu Thr Arg Glu Ser Phe Arg Leu Arg Gln His Glu Leu
                                       75
Pro Ala Met Asp Phe Val Val Val Ala Lys Lys Gly Val Ala Asp Leu
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Asp Asn Arg Ala Leu Ser Glu Ala Leu Glu Lys Leu Trp Arg Arg His
Cys Arg Leu Ala Arg Gly Ser
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65					Ile 70					75					80
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_	130				Gly Asn	135					140				
145	-				150					155					160
			_	165	Ser				170					175	
Glu	Asp	Met	Ala 180	Glu	Asp	Met	Thr	Pro 185	Leu	Tyr	Gln	Ala	Ile 190	Val	Asp
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		275			Gly		280					285			
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		355					360					365			Val
	370				Arg	375					380				
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Gln	Ala	Leu	Gly 420		Arg	Lys	Gly	Asp 425	Leu	Lys	Asn	Met	Asn 430	Pro	Asp
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Ile	Gly 450			Ser	Glu	Phe 455			Met	Thr	Ser 460	Gly	Thr	Gly	Leu
Leu 465	Tyr	Ser	Thr	Phe	Ser 470		Tyr	Asp	Asp	Val 475	Arg	Pro	Gly	Glu	Val 480

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Gly Gln Arg Gln Asn Gly Val Leu Ile Ser Asn Gly Gln Gly Lys Ala
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Val Ala Phe Ala Leu Phe Gly Leu Gln Asp Arg Gly Lys Leu Phe Leu
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Gly His Gly Ala Glu Val Tyr Glu Gly Gln Ile Ile Gly Ile His Ser
                         520
Arg Ser Asn Asp Leu Thr Val Asn Cys Leu Thr Gly Lys Lys Leu Thr
         535
                                         540
Asn Met Arg Ala Ser Gly Thr Asp Glu Ala Val Val Leu Val Pro Pro
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               550
Ile Arg Met Thr Leu Glu Gln Ala Leu Glu Phe Ile Asp Asp Asp Glu
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Leu Val Glu Val Thr Pro Thr Ser Ile Arg Ile Arg Lys Arg His
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Leu Ser Ser Asn Glu Ala Ile Asp Cys Leu Met Phe Ser Tyr Gln Met
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Glu His Pro Asp Glu His Gln Asn Val Arg Gln Leu Ile Gly Lys Leu
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His Glu Arg Gln Gln Asn Val Pro Val Phe Leu Leu Gly Asp Arg Glu
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Lys Ala Leu Ala Ala Met Asp Arg Asp Leu Leu Glu Leu Val Asp Glu
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Phe Ala Trp Ile Leu Glu Asp Thr Ala Asp Phe Ile Ala Gly Arg Ala
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Val Ala Ala Met Thr Arg Tyr Arg Gln Gln Leu Leu Pro Pro Leu Phe
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Ser Ala Leu Met Lys Tyr Ser Asp Ile His Glu Tyr Ser Trp Ala Ala
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Pro Gly His Gln Gly Gly Val Gly Phe Thr Lys Thr Pro Ala Gly Arg
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Phe Tyr His Asp Tyr Tyr Gly Glu Asn Leu Phe Arg Thr Asp Met Gly
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           180
Ile Glu Arg Thr Ser Leu Gly Ser Leu Leu Asp His Thr Gly Ala Phe
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Gly Glu Ser Glu Lys Tyr Ala Ala Arg Val Phe Gly Ala Asp Arg Ser
                                         220
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Trp Ser Val Val Val Gly Thr Ser Gly Ser Asn Arg Thr Ile Met Gln
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Ala Cys Met Thr Asp Asn Asp Val Val Val Asp Arg Asn Cys His
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Lys Ser Ile Glu Gln Gly Leu Met Leu Thr Gly Ala Lys Pro Val Tyr
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Met Val Pro Ser Arg Asn Arg Tyr Gly Ile Ile Gly Pro Ile Tyr Pro
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Gln Glu Met Gln Pro Glu Thr Leu Gln Lys Lys Ile Ser Glu Ser Pro
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Leu Thr Lys Asp Lys Ala Gly Gln Lys Pro Ser Tyr Cys Val Val Thr
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385			Leu		390					395					400
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465	_	_	Glu		470					475					480
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		675					680					685			Gly
_	690					695					700				Met
705			_		710					715					Ser 720
_		_	Ser	725					730					735	
			740	Gly	Thr	Glu	Ile	Ile 745	Asp	Gly	Ile	Tyr	His 750	Val	Met
Cys	Val	Lys 755	Ala												
<21	0> 4	27													

<210> 427 <211> 253

<212> PRT <213> Escherichia coli <400> 427 Met Arg Ile Cys Ser Asp Gln Pro Cys Ile Val Leu Leu Thr Glu Lys 10 Asp Val Trp Ile Arg Val Asn Gly Lys Glu Pro Ile Ser Leu Lys Ala Asn His Met Ala Leu Leu Asn Cys Glu Asn Asn Ile Ile Asp Val Ser 40 Ser Leu Asn Asn Thr Leu Val Ala His Ile Ser His Asp Ile Ile Lys 55 Asp Tyr Leu Arg Phe Leu Asn Lys Asp Leu Ser Gln Ile Pro Val Trp Gln Arg Ser Ala Thr Pro Ile Leu Thr Leu Pro Cys Leu Thr Pro Asp 90 Val Phe Arg Val Ala Ala Gln His Ser Met Met Pro Ala Glu Thr Glu 100 105 Ser Glu Lys Glu Arg Thr Arg Ala Leu Leu Phe Thr Val Leu Ser Arg 120 125 115 Phe Leu Asp Ser Lys Lys Phe Val Ser Leu Met Met Tyr Met Leu Arg 135 Asn Cys Val Ser Asp Ser Val Tyr Gln Ile Ile Glu Ser Asp Ile His 150 155 Lys Asp Trp Asn Leu Ser Met Val Ala Ser Cys Leu Cys Leu Ser Pro 165 170 175 Ser Leu Leu Lys Lys Lys Leu Lys Ser Glu Asn Thr Ser Tyr Ser Gln 185 180 Ile Ile Thr Thr Cys Arg Met Arg Tyr Ala Val Asn Glu Leu Met Met 200 205 Asp Gly Lys Asn Ile Ser Gln Val Ser Gln Ser Cys Gly Tyr Asn Ser 210 215 220 Thr Ser Tyr Phe Ile Ser Val Phe Lys Asp Phe Tyr Gly Met Thr Pro 230 Leu His Tyr Val Ser Gln His Arg Glu Arg Thr Val Ala <210> 428 <211> 425 <212> PRT <213> Escherichia coli <400> 428 Met Leu Arg Leu Pro Asn Ile Tyr Phe Lys Gly Tyr Ile Arg Ile Thr 10 Gln Glu Thr Asn Met Ala Thr Ala Trp Tyr Lys Gln Val Asn Pro Pro 25 Gln Arg Lys Ala Leu Phe Ser Ala Trp Leu Gly Tyr Val Phe Asp Gly 40 Phe Asp Phe Met Met Ile Phe Tyr Ile Leu His Ile Ile Lys Ala Asp 55 60 Leu Gly Ile Thr Asp Ile Gln Ala Thr Leu Ile Gly Thr Val Ala Phe 70 75 Ile Ala Arg Pro Ile Gly Gly Gly Phe Phe Gly Ala Met Ala Asp Lys 90 Tyr Gly Arg Lys Pro Met Met Trp Ala Ile Phe Ile Tyr Ser Val 105 Gly Thr Gly Leu Ser Gly Ile Ala Thr Asn Leu Tyr Met Leu Ala Val 120

Cys Arg Phe Ile Val Gly Leu Gly Met Ser Gly Glu Tyr Ala Cys Ala

135

Ser Thr Tyr Ala Val Glu Ser Trp Pro Lys Asn Leu Gln Ser Lys Ala

140

```
155
         150
Ser Ala Phe Leu Val Ser Gly Phe Ser Val Gly Asn Ile Ile Ala Ala
                                170
             165
Gln Ile Ile Pro Gln Phe Ala Glu Val Tyr Gly Trp Arg Asn Ser Phe
                            185
Phe Ile Gly Leu Leu Pro Val Leu Leu Val Leu Trp Ile Arg Lys Ser
               200
Ala Pro Glu Ser Gln Glu Trp Ile Glu Asp Lys Tyr Lys Asp Lys Ser
                    215
                                       220
Thr Phe Leu Ser Val Phe Arg Lys Pro His Leu Ser Ile Ser Met Ile
                  230
                                     235
Val Phe Leu Val Cys Phe Cys Leu Phe Gly Ala Asn Trp Pro Ile Asn
                                250 255
              245
Gly Leu Leu Pro Ser Tyr Leu Ala Asp Asn Gly Val Asn Thr Val Val
                             265
          260
Ile Ser Thr Leu Met Thr Ile Ala Gly Leu Gly Thr Leu Thr Gly Thr
                         280
Ile Phe Phe Gly Phe Val Gly Asp Lys Ile Gly Val Lys Lys Ala Phe
            295
                                       300
Val Val Gly Leu Ile Thr Ser Phe Ile Phe Leu Cys Pro Leu Phe Phe
          310 315
Ile Ser Val Lys Asn Ser Ser Leu Ile Gly Leu Cys Leu Phe Gly Leu
             325
                                 330
                                                    335
Met Phe Thr Asn Leu Gly Ile Ala Gly Leu Val Pro Lys Phe Ile Tyr
                             345
Asp Tyr Phe Pro Thr Lys Leu Arg Gly Leu Gly Thr Gly Leu Ile Tyr
                         360
                                           365
Asn Leu Gly Ala Thr Gly Gly Met Ala Ala Pro Val Leu Ala Thr Tyr
                               380
                     375
Ile Ser Gly Tyr Tyr Gly Leu Gly Val Ser Leu Phe Ile Val Thr Val
                                    395
               390
Ala Phe Ser Ala Leu Leu Ile Leu Leu Val Gly Phe Asp Ile Pro Gly
             405
                                410
Lys Ile Tyr Lys Leu Ser Val Ala Lys
<210> 429
<211> 377
<212> PRT
<213> Escherichia coli
<400> 429
Met Ile Gly Gly Phe Met Ile Asn Tyr Gly Val Val Gly Val Gly Tyr
                                10
Phe Gly Ala Glu Leu Ala Arg Phe Met Asn Met His Asp Asn Ala Lys
                             25
          20
Ile Thr Cys Val Tyr Asp Pro Glu Asn Gly Glu Asn Ile Ala Arg Glu
               40
Leu Gln Cys Ile Asn Met Ser Ser Leu Asp Ala Leu Val Ser Ser Lys
                    - 55
                                         60
Leu Val Asp Cys Val Ile Val Ala Thr Pro Asn Tyr Leu His Lys Glu
                  70
                                    75
Pro Val Ile Lys Ala Ala Lys Asn Lys Lys His Val Phe Cys Glu Lys
                                 90
              85
Pro Ile Ala Leu Ser Tyr Glu Asp Cys Val Asp Met Val Lys Ala Cys
                             105
Lys Glu Ala Gly Val Thr Phe Met Ala Gly His Ile Met Asn Phe Phe
                                           125
                          120
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Asn Gly Val Gln Tyr Ala Arg Lys Leu Ile Lys Glu Gly Val Ile Gly
                       135
Glu Ile Leu Ser Cys His Thr Lys Arg Asn Gly Trp Glu Asn Lys Gln
                                       155
Glu Arg Leu Ser Trp Lys Lys Met Lys Glu Gln Ser Gly Gly His Leu
                                  170
               165
Tyr His His Ile His Glu Leu Asp Cys Val Gln His Leu Leu Gly Glu
                              185
Ile Pro Glu Thr Val Thr Met Ile Gly Gly Asn Leu Ala His Ser Gly
                          200
Pro Gly Phe Gly Asn Glu Asp Asp Met Leu Phe Met Thr Leu Glu Phe
              215
                                          220
Pro Ser Gly Lys Leu Ala Thr Leu Glu Trp Gly Ser Ala Phe Asn Trp
                                      235
        · 230
Pro Glu His Tyr Val Ile Ile Asn Gly Thr Lys Gly Ser Ile Lys Ile
                245
                                   250
Asp Met Gln Glu Thr Ala Gly Ser Leu Arg Ile Gly Gly Gln Thr Lys
                               265
His Phe Leu Val His Glu Thr Gln Glu Glu Asp Asp Asp Arg Arg Lys
        275
                           280
Gly Asn Met Thr Ser Glu Met Asp Gly Ala Ile Ala Tyr Gly His Pro
                       295
Gly Lys Lys Thr Pro Leu Trp Leu Ala Ser Leu Ile Arg Lys Glu Thr
                    310
                                      315
Leu Phe Leu His Asn Ile Leu Cys Gly Ala Lys Pro Glu Glu Asp Tyr
                                  330
               325
Ile Asp Leu Leu Asn Gly Glu Ala Ala Met Ser Ala Ile Ala Thr Ala
                               345
           340
Asp Ala Ala Thr Leu Ser Arg Ser Gln Asp Arg Lys Val Lys Ile Ser
                           360
       355
Glu Ile Ile Lys His Thr Ser Val Met
. 370
                        375
<210> 430
<211> 464
<212> PRT
<213> Escherichia coli
<400> 430
Met Ser Ala Gly Lys Leu Pro Glu Gly Trp Val Ile Ala Pro Val Ser
                                   10
Thr Val Thr Thr Leu Ile Arg Gly Val Thr Tyr Lys Lys Glu Gln Ala
                               25
Ile Asn Tyr Leu Lys Asp Asp Tyr Leu Pro Leu Ile Arg Ala Asn Asn
                            40
Ile Gln Asn Gly Lys Phe Asp Thr Thr Asp Leu Val Phe Val Pro Lys
                       55
Asn Leu Val Lys Glu Ser Gln Lys Ile Ser Pro Glu Asp Ile Val Ile
                    70
Ala Met Ser Ser Gly Ser Lys Ser Val Val Gly Lys Ser Ala His Gln
                                   90
His Leu Pro Phe Glu Cys Ser Phe Gly Ala Phe Cys Gly Val Leu Arg
            100
                               105
Pro Glu Lys Leu Ile Phe Ser Gly Phe Ile Ala His Phe Thr Lys Ser
                           120
                                              125
       115
Ser Leu Tyr Arg Asn Lys Ile Ser Ser Leu Ser Ala Gly Ala Asn Ile
                       135
                                           140
Asn Asn Ile Lys Pro Ala Ser Phe Asp Leu Ile Asn Ile Pro Ile Pro
                    150
                                    155
Pro Leu Ala Glu Gln Lys Ile Ile Ala Glu Lys Leu Asp Thr Leu Leu
```

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170
               165
Ala Gln Val Asp Ser Thr Lys Ala Arg Phe Glu Gln Ile Pro Gln Ile
                             185
          180
Leu Lys Arg Phe Arg Gln Ala Val Leu Gly Gly Ala Val Asn Gly Lys
                          200
Leu Thr Glu Lys Trp Arg Asn Phe Glu Pro Gln His Ser Val Phe Lys
                                      220
                     215
Lys Leu Asn Phe Glu Ser Ile Leu Thr Glu Leu Arg Asn Gly Leu Ser
         230
                                    235
Ser Lys Pro Asn Glu Ser Gly Val Gly His Pro Ile Leu Arg Ile Ser
           245
                                  250
Ser Val Arg Ala Gly His Val Asp Gln Asn Asp Ile Arg Phe Leu Glu
                              265
Cys Ser Glu Ser Glu Leu Asn Arg His Lys Leu Gln Asp Gly Asp Leu
                                             285
                          280
Leu Phe Thr Arg Tyr Asn Gly Ser Leu Glu Phe Val Gly Val Cys Gly
                      295
                                         300
Leu Leu Lys Lys Leu Gln His Gln Asn Leu Leu Tyr Pro Asp Lys Leu
                                      315
                  310
Ile Arg Ala Arg Leu Thr Lys Asp Ala Leu Pro Glu Tyr Ile Glu Ile
                                 330
              325
Phe Phe Ser Ser Pro Ser Ala Arg Asn Ala Met Met Asn Cys Val Lys
           340 345
Thr Thr Ser Gly Gln Lys Gly Ile Ser Gly Lys Asp Ile Lys Ser Gln
                          360
Val Val Leu Leu Pro Pro Val Lys Glu Gln Ala Glu Ile Val Arg Arg
                                          380
                       375
Val Glu Gln Leu Phe Ala Tyr Ala Asp Thr Ile Glu Lys Gln Val Asn
                   390
                                   395
Asn Ala Leu Ala Arg Val Asn Asn Leu Thr Gln Ser Ile Leu Ala Lys
                    410
              405
Ala Phe Arg Gly Glu Leu Thr Ala Gln Trp Arg Ala Glu Asn Pro Asp
                             425
           420
Leu Ile Ser Gly Glu Asn Ser Ala Ala Ala Leu Leu Glu Lys Ile Lys
                          440
Ala Glu Arg Ala Ala Ser Gly Gly Lys Lys Ala Ser Arg Lys Lys Ser
                      455
<210> 431
<211> 529
<212> PRT
<213> Escherichia coli
Met Asn Asn Asp Leu Val Ala Lys Leu Trp Lys Leu Cys Asp Asn
                                  10
Leu Arg Asp Gly Gly Val Ser Tyr Gln Asn Tyr Val Asn Glu Leu Ala
                               25
           20
Ser Leu Leu Phe Leu Lys Met Cys Lys Glu Thr Gly Gln Glu Ala Glu
                           40
Tyr Leu Pro Glu Gly Tyr Arg Trp Asp Asp Leu Lys Ser Arg Ile Gly
                       55
                                         60
Gln Glu Gln Leu Gln Phe Tyr Arg Lys Met Leu Val His Leu Gly Glu
                   70
                                      75
Asp Asp Lys Lys Leu Val Gln Ala Val Phe His Asn Val Ser Thr Thr
                                  90
               85
Ile Thr Glu Pro Lys Gln Ile Thr Ala Leu Val Ser Asn Met Asp Ser
                                                 110
                               105
Leu Asp Trp Tyr Asn Gly Ala His Gly Lys Ser Arg Asp Asp Phe Gly
                           120
                                              125
```

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Asp Met Tyr Glu Gly Leu Leu Gln Lys Asn Ala Asn Glu Thr Lys Ser
                       135
Gly Ala Gly Gln Tyr Phe Thr Pro Arg Pro Leu Ile Lys Thr Ile Ile
                   150
                                      155
His Leu Leu Lys Pro Gln Pro Arg Glu Val Val Gln Asp Pro Ala Ala
                                 170
               165
Gly Thr Ala Gly Phe Leu Ile Glu Ala Asp Arg Tyr Val Lys Ser Gln
          180
                              185
Thr Asn Asp Leu Asp Asp Leu Asp Gly Asp Thr Gln Asp Phe Gln Ile
                 200
His Arg Ala Phe Ile Gly Leu Glu Leu Val Pro Gly Thr Arg Arg Leu
            215
                                          220
Ala Leu Met Asn Cys Leu Leu His Asp Ile Glu Gly Asn Leu Asp His
                                   235
        230
Gly Gly Ala Ile Arg Leu Gly Asn Thr Leu Gly Ser Asp Gly Glu Asn
                                  250
Leu Pro Lys Ala His Ile Val Ala Thr Asn Pro Pro Phe Gly Ser Ala
                               265
                                               270
Ala Gly Thr Asn Ile Thr Arg Thr Phe Val His Pro Thr Ser Asn Lys
                           280
Gln Leu Cys Phe Met Gln His Ile Ile Glu Thr Leu His Pro Gly Gly
                       295
Arg Ala Ala Val Val Pro Asp Asn Val Leu Phe Glu Gly Gly Lys
                   310
                                     315
Gly Thr Asp Ile Arg Arg Asp Leu Met Asp Lys Cys His Leu His Thr
              325
                                  330
Ile Leu Arg Leu Pro Thr Gly Ile Phe Tyr Ala Gln Gly Val Lys Thr
                               345
           340
Asn Val Leu Phe Phe Thr Lys Gly Thr Val Ala Asn Pro Asn Gln Asp
                           360
Lys Asn Cys Thr Asp Asp Val Trp Val Tyr Asp Leu Arg Thr Asn Met
                       375
                                          380
Pro Ser Phe Gly Lys Arg Thr Pro Phe Thr Asp Glu His Leu Gln Pro
                                     395
                   390
Phe Glu Arg Val Tyr Gly Glu Asp Pro His Gly Leu Ser Pro Arg Thr
              405
                                 410
Glu Gly Glu Trp Ser Phe Asn Ala Glu Glu Thr Glu Val Ala Asp Ser
                              425
Glu Glu Asn Lys Asn Thr Asp Gln His Leu Ala Thr Ser Arg Trp Arg
                          440
                                             445
Lys Phe Ser Arg Glu Trp Ile Arg Thr Ala Lys Ser Asp Ser Leu Asp
                                          460
                      455
Ile Ser Trp Leu Lys Asp Lys Asp Ser Ile Asp Ala Asp Ser Leu Pro
                                      475
                   470
Glu Pro Asp Val Leu Ala Ala Glu Ala Met Gly Glu Leu Val Gln Ala
               485
                                  490
Leu Ser Glu Leu Asp Ala Leu Met Arg Glu Leu Gly Ala Ser Asp Glu
                              505
Ala Asp Leu Gln Arg Gln Leu Leu Glu Glu Ala Phe Gly Gly Val Lys
Glu
```

<400> 432

Met Lys Lys Glu Asn Tyr Ser Phe Lys Gln Ala Cys Ala Val Val Gly

<sup>&</sup>lt;210> 432

<sup>&</sup>lt;211> 98

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Escherichia coli

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10
Gly Gln Ser Ala Met Ala Arg Leu Leu Gly Val Ser Pro Pro Ser Val
Asn Gln Trp Ile Lys Gly Val Arg Gln Leu Pro Ala Glu Arg Cys Pro
                            40
Ala Ile Glu Arg Ala Thr Arg Gly Glu Val Leu Cys Glu Glu Leu Arg
                       55
Pro Asp Ile Asp Trp Ser Tyr Leu Arg Arg Ser Ala Cys Cys Ser Gln
                   70
Asn Met Ser Val Lys Gln Leu Asn Asp Ser Asn Lys Ser Ser Phe Asp
His Thr
<210> 433
<211> 140
<212> PRT
<213> Escherichia coli
<400> 433
Met Lys Ile Lys His Glu His Ile Glu Ser Val Leu Phe Ala Leu Ala
                                    10
Ala Glu Lys Gly Gln Ala Trp Val Ala Asn Ala Ile Thr Glu Glu Tyr
                               25
            20
Leu Arg Gln Gly Gly Glu Leu Pro Leu Val Pro Gly Lys Asp Trp
                           40
Asn Asn Gln Gln Asn Ile Tyr His Arg Trp Leu Lys Gly Glu Thr Lys
                       55
                                        60
Thr Gln Arg Glu Lys Ile Gln Lys Leu Ile Pro Ala Ile Leu Ala Ile
                   70
                                      75
Leu Pro Arg Glu Leu Arg His Arg Leu Cys Ile Phe Asp Thr Leu Glu
                                   90
               85
Arg Arg Ala Leu Leu Ala Ala Gln Glu Ala Leu Ser Thr Ala Ile Asp
                               105
Ala His Asp Asp Ala Val Gln Ala Val Tyr Arg Lys Ala His Phe Ser
                            120
Gly Gly Gly Ser Ser Asp Asp Ser Val Ile Val His
    130
                        135
<210> 434
<211> 285
<212> PRT
<213> Escherichia coli
<400> 434
Met Leu Phe Val Leu Ile Leu Ser His Arg Ala Ala Ser Tyr Gly Ala
                                    10
Ile Met Ala Ala Leu Pro Tyr Met Gln Leu Tyr Ile Ala Asp Tyr Leu
Ala Asp Thr Met His Leu Ser Ala Glu Glu His Gly Ala Tyr Leu Leu
Leu Met Phe Asn Tyr Trp Gln Thr Gly Lys Pro Ile Pro Lys Asn Arg
                        55
Leu Ala Lys Ile Ala Arg Leu Thr Asn Glu Arg Trp Ala Asp Val Glu
                    70
Pro Ser Leu Gln Glu Phe Phe Cys Asp Asn Gly Glu Glu Trp Val His
Leu Arg Ile Glu Glu Ásp Leu Ala Ser Val Arg Glu Lys Leu Thr Lys
                               105
Lys Ser Ala Ala Gly Lys Ala Ser Val Gln Ala Arg Arg Ser Arg Lys
```

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120
      115
Glu Ala Asp Val Gln Thr Lys Gln Glu Arg Asn Leu Thr Gly Val Gln
            135
                                        140
Thr Asp Val Glu Val Val Phe Glu His Asp Val Asn Thr Lys Ala Thr
                  150
Asn Lys Asp Thr Asp Lys Asp Leu Lys Thr Asp Pro Pro Leu Asn Pro
            165
                                170
Pro Arg Gly Asn Arg Gly Val Lys Lys Phe Asp Pro Leu Asp Ile Thr
                   185
                                      190
          180
Leu Pro Asn Trp Ile Ser Val Ser Leu Trp Arg Glu Trp Val Glu Phe
                          200
Arg Gln Ala Leu Arg Lys Pro Ile Arg Thr Glu Gln Gly Ala Asn Gly
                       215
Ala Ile Arg Glu Leu Glu Lys Phe Arg Gln Gly Phe Ser Pro Glu
                   230
                                      235
Gln Val Ile Arg His Ser Ile Ala Asn Glu Tyr Gln Gly Leu Phe Ala
                                 250
               245
Pro Lys Gly Val Arg Pro Glu Thr Leu Leu Arg Gln Val Asn Thr Val
                             265
Ser Leu Pro Asp Ser Ala Ile Pro Pro Gly Phe Arg Gly
                          280
<210> 435
<211> 248
<212> PRT
<213> Escherichia coli
<400> 435
Met Lys Asn Ile Ala Thr Gly Asp Val Leu Glu Arg Ile Arg Arg Leu
Ala Pro Ser His Val Thr Ala Pro Phe Lys Thr Val Ala Glu Trp Arg
          20
                              25
Glu Trp Gln Leu Ser Glu Gly Gln Lys Arg Cys Glu Glu Ile Asn Arg
Gln Asn Arg Gln Leu Arg Val Glu Lys Ile Leu Asn Arg Ser Gly Ile
                     55
Gln Pro Leu His Arg Lys Cys Ser Phe Ser Asn Tyr Gln Val Gln Asn
                   70
                                     75
Glu Gly Gln Arg Tyr Ala Leu Ser Gln Ala Lys Ser Ile Ala Asp Glu
              85
                                  90
Leu Met Thr Gly Cys Thr Asn Phe Ala Phe Ser Gly Lys Pro Gly Thr
                              105
Gly Lys Asn His Leu Ala Ala Ile Gly Asn Arg Leu Leu Lys Asp
                                             125
                          120
Gly Gln Thr Val Ile Val Val Thr Val Ala Asp Val Met Ser Ala Leu
                      135
                                         140
His Ala Ser Tyr Asp Asp Gly Gln Ser Gly Glu Lys Phe Leu Arg Glu
                  150
                                     155
Leu Cys Glu Val Asp Leu Leu Val Leu Asp Glu Ile Gly Ile Gln Arg
              165
                                 170
                                                    175
Glu Thr Lys Asn Glu Gln Val Val Leu His Gln Ile Val Asp Arg Arg
          180
                             185
Thr Ala Ser Met Arg Ser Val Gly Met Leu Thr Asn Leu Asn Tyr Glu
                          200
Ala Met Lys Thr Leu Leu Gly Glu Arg Ile Met Asp Arg Met Thr Met
                      215
                                         220
Asn Gly Gly Arg Trp Val Asn Phe Asn Trp Glu Ser Trp Arg Pro Asn
                  230
                                    235
Val Val Gln Pro Gly Ile Ala Lys
               245
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<210> 436
<211> 203
<212> PRT
<213> Escherichia coli
<400> 436
Met Ser Ser Ser Gln Glu Leu Arg Ser Asn Phe Tyr Arg Glu Lys Asn
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Leu Met Glu Thr Val Phe Asp Ala Leu Lys Ala Met Gly Lys Ala Thr
  20
                        25
Ser Ile Glu Leu Ala Ala Arg Leu Asp Ile Ser Arg Glu Glu Val Leu
                        40
Asn Glu Leu Trp Glu Leu Lys Lys Ala Gly Phe Val Asp Lys Ser Ala
                    55
                                    60
Tyr Thr Trp Arg Val Ala Asp Asn Asn Val Gln Gln Glu Gln Pro Ala
               70
                                 75
Gln Ala Glu Leu Pro Glu Glu Ile Thr Thr Ala Thr Val Ala Lys Ile
                               90
           85
Ser Glu Cys Asp Leu Thr Ala Thr Ile Glu Gln Arg Gly Pro Gln Thr
                           105
Ala Asp Glu Leu Ala Thr Leu Phe Gly Thr Thr Ser Arg Lys Val Ala
                        120
                                 125
Ser Thr Leu Ala Met Ala Ile Ser Lys Gly Arg Leu Ile Arg Val Asn
                    135
                                      140
Gln Gly Gly Lys Phe Arg Tyr Cys Ile Pro Gly Asp Asn Leu Pro Ala
145 150
                                   155
Glu Pro Lys Ala Ala Ser Val Ser Pro Leu Trp Leu Ser Ala Ser Ser
                      170 175
             165
Ser Ala Cys His Gly Val Leu Ile Ile Thr Val Ile Thr Pro Ser Pro
         180 185 190
Thr Lys Asn Ser Ala Thr Lys Met Pro Glu Asn
 195
                        200
<210> 437
<211> 101
<212> PRT
<213> Escherichia coli
<400> 437
Met Gln Met Arg Gln Arg Asp Val Ala Ala Leu Asp Ala Lys Tyr Thr
                                10
              5
Lys Glu Leu Ala Asp Ala Lys Ala Glu Asn Asp Ala Leu Arg Asp Asp
                            25
Val Ala Ala Gly Arg Arg Leu His Ile Lys Ala Val Cys Gln Ser
                         40
                                          45
Val Arg Glu Ala Thr Thr Ala Ser Gly Val Asp Asn Ala Ala Ser Pro
                    55
Arg Leu Ala Asp Thr Ala Glu Arg Asp Tyr Phe Thr Leu Arg Glu Arg
                70
Leu Val Met Met Gln Ala Gln Leu Glu Gly Ala Gln Gln Tyr Ile Thr
                               90
                                                  95
             85
Glu Gln Cys Leu Lys
          100
<210> 438
<211> 292
<212> PRT
<213> Escherichia coli
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<400> 438
Met Lys Leu Gly Phe Ile Gly Leu Gly Ile Met Gly Thr Pro Met Ala
Ile Asn Leu Ala Arg Ala Gly His Gln Leu His Val Thr Thr Ile Gly
           20
                              25
Pro Val Ala Asp Glu Leu Leu Ser Leu Gly Ala Val Ser Val Glu Thr
                          40
Ala Arg Gln Val Thr Glu Ala Ser Asp Ile Ile Phe Ile Met Val Pro
                      55
                                          60
Asp Thr Pro Gln Val Glu Glu Val Leu Phe Gly Glu Asn Gly Cys Thr
                                    75
                  70
Lys Ala Ser Leu Lys Gly Lys Thr Ile Val Asp Met Ser Ser Ile Ser
                               90
              85
Pro Ile Glu Thr Lys Arg Phe Ala Arg Gln Val Asn Glu Leu Gly Gly
          100
                              105
Asp Tyr Leu Asp Ala Pro Val Ser Gly Gly Glu Ile Gly Ala Arg Glu
                           120
                                              125
Gly Thr Leu Ser Ile Met Val Gly Gly Asp Glu Ala Val Phe Glu Arg
                       135
                                          140
Val Lys Pro Leu Phe Glu Leu Leu Gly Lys Asn Ile Thr Leu Val Gly
                   150
                                      155
Gly Asn Gly Asp Gly Gln Thr Cys Lys Val Ala Asn Gln Ile Ile Val
                                  170
Ala Leu Asn Ile Glu Ala Val Ser Glu Ala Leu Leu Phe Ala Ser Lys
                                                 190
           180
                              185
Ala Gly Ala Asp Pro Val Arg Val Arg Gln Ala Leu Met Gly Gly Phe
                          200
Ala Ser Ser Arg Ile Leu Glu Val His Gly Glu Arg Met Ile Lys Arg
                       215
                                          220
Thr Phe Asn Pro Gly Phe Lys Ile Ala Leu His Gln Lys Asp Leu Asn
                   230
                                      235
Leu Ala Leu Gln Ser Ala Lys Ala Leu Ala Leu Asn Leu Pro Asn Thr
                    250
              245
Ala Thr Cys Gln Glu Leu Phe Asn Thr Cys Ala Ala Asn Gly Gly Ser
                 265
Gln Leu Asp His Ser Ala Leu Val Gln Ala Leu Glu Leu Met Ala Asn
His Lys Leu Ala
   290
<210> 439
<211> 92
<212> PRT
<213> Escherichia coli
<400> 439
Met Asn Arg Pro Ala Ile Leu Lys Lys Lys Ala Ala Lys Asp Val Ala
                                  10
Ser Val Leu Lys Ile Ile Phe Leu Phe Tyr Leu Phe Leu Ile Ala Arg
           20
                               25
Leu Lys Gln Arg Tyr Ser Ile Arg Glu Ile Lys Arg Asp Leu Trp Asn
                           40
Ile Arg Glu Asn Tyr Ser Ser Asn Ala Ala Ile Ala Lys Ile Tyr Cys
                       55
                                          60
Arg Lys Arg Lys Ala Ser Gly Pro Gly Lys His Leu Thr Ile Leu Pro
                   70
                                      75
Tyr Gly Trp Val Arg Phe Ile Thr Phe Pro Ile Met
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<210> 440

<211> 437

<212> PRT <213> Escherichia coli <400> 440 Met Val Gly Gly Phe Phe Ile Leu Gly Leu Ser Thr Phe Ser Ile Met 10 Leu Ala Ile Ile Leu Ser Ala Phe Phe Ile Ala Ala Val Met Val Leu 20 25 Asn Gly Ala Ala Gly Ser Lys Tyr Gly Val Pro Phe Ala Met Ile Leu 35 . 40 4.5 Arg Ala Ser Tyr Gly Val Arg Gly Ala Leu Phe Pro Gly Leu Leu Arg 55 Gly Gly Ile Ala Ala Ile Met Trp Phe Gly Leu Gln Cys Tyr Ala Gly 70 75 Ser Leu Ala Cys Leu Ile Leu Ile Gly Lys Ile Trp Pro Gly Phe Leu 90 85 Thr Leu Gly Gly Asp Phe Thr Leu Leu Gly Leu Ser Leu Pro Gly Leu 105 Ile Thr Phe Leu Ile Phe Trp Leu Val Asn Val Gly Ile Gly Phe Gly 120 125 Gly Gly Lys Val Leu Asn Lys Phe Thr Ala Ile Leu Asn Pro Cys Ile 135 140 Tyr Ile Val Phe Gly Gly Met Ala Ile Trp Ala Ile Ser Leu Val Gly 150 155 Ile Gly Pro Ile Phe Asp Tyr Ile Pro Ser Gly Ile Gln Lys Ala Glu 170 175 165 Asn Gly Gly Phe Leu Phe Leu Val Val Ile Asn Ala Val Val Ala Val 185 190 180 Trp Ala Ala Pro Ala Val Ser Ala Ser Asp Phe Thr Gln Asn Ala His 200 Ser Phe Arg Glu Gln Ala Leu Gly Gln Thr Leu Gly Leu Val Val Ala 210 215 220 Tyr Ile Leu Phe Ala Val Ala Gly Val Cys Ile Ile Ala Gly Ala Ser 225 230 235 Ile His Tyr Gly Ala Asp Thr Trp Asn Val Leu Asp Ile Val Gln Arg 245 250 255 Trp Asp Ser Leu Phe Ala Ser Phe Phe Ala Val Leu Val Ile Leu Met 260 265 Thr Thr Ile Ser Thr Asn Ala Thr Gly Asn Ile Ile Pro Ala Gly Tyr 275 280 Gln Ile Ala Ala Ile Ala Pro Thr Lys Leu Thr Tyr Lys Asn Gly Val 300 295 Leu Ile Ala Ser Ile Ile Ser Leu Leu Ile Cys Pro Trp Lys Leu Met 310 315 Glu Asn Gln Asp Ser Ile Tyr Leu Phe Leu Asp Ile Ile Gly Gly Met 325 330 Leu Gly Pro Val Ile Gly Val Met Met Ala His Tyr Phe Val Val Met 345 340 Arg Gly Gln Ile Asn Leu Asp Glu Leu Tyr Thr Ala Pro Gly Asp Tyr 360 365 Lys Tyr Tyr Asp Asn Gly Phe Asn Leu Thr Ala Phe Ser Val Thr Leu 375 380 Val Ala Val Ile Leu Ser Leu Gly Gly Lys Phe Ile His Phe Met Glu 390 395 Pro Leu Ser Arg Val Ser Trp Phe Val Gly Val Ile Val Ala Phe Ala 410 ......415 405 Ala Tyr Ala Leu Leu Lys Lys Arg Thr Thr Ala Glu Lys Thr Gly Glu 425 420 Gln Lys Thr Ile Gly

435

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Ile Ser Ala Gly Asp Arg Val Val Thr Asp Gly Ile Asp Arg Leu Thr 425 Glu Gly Ala Lys Val Glu Val Val Glu Ala Gln Ser Ala Thr Thr Pro 440 Glu Glu Lys Ala Thr Ser Arg Glu Tyr Ala Lys Lys Gly Ala Arg Ser <210> 442 <211> 1040 <212> PRT <213> Escherichia coli <400> 442 Met Gln Val Leu Pro Pro Ser Ser Thr Gly Gly Pro Ser Arg Leu Phe 10 Ile Met Arg Pro Val Ala Thr Thr Leu Leu Met Val Ala Ile Leu Leu Ala Gly Ile Ile Gly Tyr Arg Ala Leu Pro Val Ser Ala Leu Pro Glu 40 Val Asp Tyr Pro Thr Ile Gln Val Val Thr Leu Tyr Pro Gly Ala Ser 55 60 Pro Asp Val Met Thr Ser Ala Val Thr Ala Pro Leu Glu Arg Gln Phe 70 ... 75 Gly Gln Met Ser Gly Leu Lys Gln Met Ser Ser Gln Ser Ser Gly Gly 90 Ala Ser Val Ile Thr Leu Gln Phe Gln Leu Thr Leu Pro Leu Asp Val 100 105 110 Ala Glu Gln Glu Val Gln Ala Ala Ile Asn Ala Ala Thr Asn Leu Leu 120 125 Pro Ser Asp Leu Pro Asn Pro Pro Val Tyr Ser Lys Val Asn Pro Ala 135 Asp Pro Pro Ile Met Thr Leu Ala Val Thr Ser Thr Ala Met Pro Met 150 155 Thr Gln Val Glu Asp Met Val Glu Thr Arg Val Ala Gln Lys Ile Ser 165 170 Gln Ile Ser Gly Val Gly Leu Val Thr Leu Ser Gly Gly Gln Arg Pro 180 185 Ala Val Arg Val Lys Leu Asn Ala Gln Ala Ile Ala Ala Leu Gly Leu 200 195 Thr Ser Glu Thr Val Arg Thr Ala Ile Thr Gly Ala Asn Val Asn Ser 215 220 Ala Lys Gly Ser Leu Asp Gly Pro Ser Arg Ala Val Thr Leu Ser Ala 230 235 Asn Asp Gln Met Gln Ser Ala Glu Glu Tyr Arg Gln Leu Ile Ile Ala 245 250 Tyr Gln Asn Gly Ala Pro Ile Arg Leu Gly Asp Val Ala Thr Val Glu 265 Gln Gly Ala Glu Asn Ser Trp Leu Gly Ala Trp Ala Asn Lys Glu Gln 280 285 Ala Ile Val Met Asn Val Gln Arg Gln Pro Gly Ala Asn Ile Ile Ser 295 300 Thr Ala Asp Ser Ile Arg Gln Met Leu Pro Gln Leu Thr Glu Ser Leu 310 315 Pro Lys Ser Val Lys Val Thr Val Leu Ser Asp Arg Thr Thr Asn Ile 325 330 Arg Ala Ser Val Asp Asp Thr Gln Phe Glu Leu Met Met Ala Ile Ala 345 Leu Val Val Met Ile Ile Tyr Leu Phe Leu Arg Asn Ile Pro Ala Thr 360 365 Ile Ile Pro Gly Val Ala Val Pro Leu Ser Leu Ile Gly Thr Phe Ala

Val Met Val Phe Leu Asp Phe Ser Ile Asn Asn Leu Thr Leu Met Ala Leu Thr Ile Ala Thr Gly Phe Val Val Asp Asp Ala Ile Val Val Ile Glu Asn Ile Ser Arg Tyr Ile Glu Lys Gly Glu Lys Pro Leu Ala Ala Ala Leu Lys Gly Ala Gly Glu Ile Gly Phe Thr Ile Ile Ser Leu Thr Phe Ser Leu Ile Ala Val Leu Ile Pro Leu Leu Phe Met Gly Asp Ile Val Gly Arg Leu Phe Arg Glu Phe Ala Ile Thr Leu Ala Val Ala Ile Leu Ile Ser Ala Val Val Ser Leu Thr Leu Thr Pro Met Met Cys Ala Arq Met Leu Ser Gln Glu Ser Leu Arg Lys Gln Asn Arg Phe Ser Arg Ala Ser Glu Lys Met Phe Asp Arg Ile Ile Ala Ala Tyr Gly Arg Gly Leu Ala Lys Val Leu Asn His Pro Trp Leu Thr Leu Ser Val Ala Leu Ser Thr Leu Leu Ser Val Leu Leu Trp Val Phe Ile Pro Lys Gly Phe Phe Pro Val Gln Asp Asn Gly Ile Ile Gln Gly Thr Leu Gln Ala Pro Gln Ser Ser Phe Ala Asn Met Ala Gln Arg Gln Arg Gln Val Ala Asp Val Ile Leu Gln Asp Pro Ala Val Gln Ser Leu Thr Ser Phe Val Gly Val Asp Gly Thr Asn Pro Ser Leu Asn Ser Ala Arg Leu Gln Ile Asn Leu Lys Pro Leu Asp Glu Arg Asp Asp Arg Val Gln Lys Val Ile Ala Arg Leu Gln Thr Ala Val Asp Lys Val Pro Gly Val Asp Leu Phe Leu Gln Pro Thr Gln Asp Leu Thr Ile Asp Thr Gln Val Ser Arg Thr Gln Tyr Gln Phe Thr Leu Gln Ala Thr Ser Leu Asp Ala Leu Ser 675 680 685 Thr Trp Val Pro Gln Leu Met Glu Lys Leu Gln Gln Leu Pro Gln Leu Ser Asp Val Ser Ser Asp Trp Gln Asp Lys Gly Leu Val Ala Tyr Val Asn Val Asp Arg Asp Ser Ala Ser Arg Leu Gly Ile Ser Met Ala Asp Val Asp Asn Ala Leu Tyr Asn Ala Phe Gly Gln Arg Leu Ile Ser Thr Ile Tyr Thr Gln Ala Asn Gln Tyr Arg Val Val Leu Glu His Asn Thr Glu Asn Thr Pro Gly Leu Ala Ala Leu Asp Thr Ile Arg Leu Thr Ser Ser Asp Gly Gly Val Val Pro Leu Ser Ser Ile Ala Lys Ile Glu Gln Arg Phe Ala Pro Leu Ser Ile Asn His Leu Asp Gln Phe Pro Val Thr Thr Ile Ser Phe Asn Val Pro Asp Asn Tyr Ser Leu Gly Asp Ala Val Gln Ala Ile Met Asp Thr Glu Lys Thr Leu Asn Leu Pro Val Asp Ile Thr Thr Gln Phe Gln Gly Ser Thr Leu Ala Phe Gln Ser Ala Leu Gly

```
855
Ser Thr Val Trp Leu Ile Val Ala Ala Val Val Ala Met Tyr Ile Val
        870
                         875
Leu Gly Ile Leu Tyr Glu Ser Phe Ile His Pro Ile Thr Ile Leu Ser
                    890 895
            885
Thr Leu Pro Thr Ala Gly Val Gly Ala Leu Leu Ala Leu Leu Ile Ala
                          905
Gly Ser Glu Leu Asp Val Ile Ala Ile Ile Gly Ile Ile Leu Leu Ile
  915 920
Gly Ile Val Lys Lys Asn Ala Ile Met Met Ile Asp Phe Ala Leu Ala
  930 935
                                    940
Ala Glu Arg Glu Gln Gly Met Ser Pro Arg Glu Ala Ile Tyr Gln Ala
                950
                                 955
Cys Leu Leu Arg Phe Arg Pro Ile Leu Met Thr Thr Leu Ala Ala Leu
             965
                             970
Leu Gly Ala Leu Pro Leu Met Leu Ser Thr Gly Val Gly Ala Glu Leu
                          985
Arg Arg Pro Leu Gly Ile Gly Met Val Gly Gly Leu Ile Val Ser Gln
                      1000 1005
Val Leu Thr Leu Phe Thr Thr Pro Val Ile Tyr Leu Leu Phe Asp Arg
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Leu Ala Leu Trp Thr Lys Ser Arg Phe Ala Arg His Glu Glu Glu Ala
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Pro Val Ala Pro Leu Pro Gln Val Asp Phe Pro Val Ile Ile Val Ser
                               45
                    40
Ala Ser Leu Pro Gly Ala Ser Pro Glu Thr Met Ala Ser Ser Val Ala
          55
                                 60
Thr Pro Leu Glu Arg Ser Leu Gly Arg Ile Ala Gly Val Ser Glu Met
Thr Ser Ser Ser Leu Gly Ser Thr Arg Ile Ile Leu Gln Phe Asp
                              90
Phe Asp Arg Asp Ile Asn Gly Ala Ala Arg Asp Val Gln Ala Ala Ile
                         105
          100
Asn Ala Ala Gln Ser Leu Leu Pro Ser Gly Met Pro Ser Arg Pro Thr
                       120
Tyr Arg Lys Ala Asn Pro Ser Asp Ala Pro Ile Met Ile Leu Thr Leu
                    135
                                     140
Thr Ser Asp Thr Tyr Ser Gln Gly Glu Leu Tyr Asp Phe Ala Ser Thr
               150
                                 155
Gln Leu Ala Pro Thr Ile Ser Gln Ile Asp Gly Val Gly Asp Val Asp
                              170
             165 .
Val Gly Gly Ser Ser Leu Pro Ala Val Arg Val Gly Leu Asn Pro Gln
         180
                        185
                                           190
Ala Leu Phe Asn Gln Gly Val Ser Leu Asp Asp Val Arg Thr Ala Val
                       200
                               · 205
Ser Asn Ala Asn Val Arg Lys Pro Gln Gly Ala Leu Glu Asp Gly Thr
                                   220
                    215
His Arg Trp Gln Ile Gln Thr Asn Asp Glu Leu Lys Thr Ala Ala Glu
                 230
                                235
```

Tyr	Gln	Pro	Leu	Ile 245	Ile	His	Tyr	Asn	Asn 250	Gly	Gly	Ala	Val	Arg 255	Leu
Gly	Asp	Val	Ala 260	Thr	Val	Thr	Asp	Ser 265	Val	Gln	Asp	Val	Arg 270	Asn	Ala
Gly	Met	Thr 275	Asn	Ala	Lys	Pro	Ala 280	Ile	Leu	Leu	Met	Ile 285	Arg	Lys	Leu
	290		Asn			295					300				
305			Gln		310					315	_				320
	-	_	Ser	325			_		330					335	
			Ile 340 Gly					345					350		
	_	355	Gly				360					365			
	370		Ser			375					380	_			
385					390					395		_			400
-	-		Ile	405					410		-			415	
GIÀ	мет	rÀz	Pro 420	Leu	GIN	Ala	нта	425	GIN	GIA	THE	Arg	430	vaı	GIÀ
		435	Leu				440					445			
	450		Met	_	_	455		_	_		460	_			
465			Ser		470					475					480
			Met	485					490					495	
		_	Arg 500			_		505	_				510		
	_	515	Gly				520					525		_	
	530		Val			535					540		-		-
545			Pro	_	550					555	_		_		560
	_	_	Ile	565		_			570					575	_
-	_		Gln 580	_			_	585		-	-	_	590		
_		595	Thr	_			600	_		_		605		_	
	610		Thr			615					620				
625			Asp		630					635					640
			Leu	645				_	650				_	655	
			Ser 660					665					670		
	_	675	Trp			-	680	_	-	-		685			
	690		Asp			695					700				
Asn 705	Leu	Val	Tyr	Asp	Arg 710	Asp	Thr	Met	Ala	Arg 715	Leu	Gly	Ile	Asp	Val 720

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Gln Ala Ala Asn Ser Leu Leu Asn Asn Ala Phe Gly Gln Arg Gln Ile
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                    730
Ser Thr Ile Tyr Gln Pro Met Asn Gln Tyr Lys Val Val Met Glu Val
          740
                             745
Asp Pro Arg Tyr Thr Gln Asp Ile Ser Ala Leu Glu Lys Met Phe Val
                         760
Ile Asn Asn Glu Gly Lys Ala Ile Pro Leu Ser Tyr Phe Ala Lys Trp
                      775
                                        780
Gln Pro Ala Asn Ala Pro Leu Ser Val Asn His Gln Gly Leu Ser Ala
                 790 795
Ala Ser Thr Ile Ser Phe Asn Leu Pro Thr Gly Lys Ser Leu Ser Asp
                                810
              805
Ala Ser Ala Ala Ile Asp Arg Ala Met Thr Gln Leu Gly Val Pro Ser
                             825
Thr Val Arg Gly Ser Phe Ala Gly Thr Ala Gln Val Phe Gln Glu Thr
                         840
                                           845
Met Asn Ser Gln Val Ile Leu Ile Ile Ala Ala Ile Ala Thr Val Tyr
                     855
                                        860
Ile Val Leu Gly Ile Leu Tyr Glu Ser Tyr Val His Pro Leu Thr Ile
                 870
                                    875
Leu Ser Thr Leu Pro Ser Ala Gly Val Gly Ala Leu Leu Ala Leu Glu
             885
                                890
Leu Phe Asn Ala Pro Phe Ser Leu Ile Ala Leu Ile Gly Ile Met Leu
        900 .905
Leu Ile Gly Ile Val Lys Lys Asn Ala Ile Met Met Val Asp Phe Ala
                         920
Leu Glu Ala Gln Arg His Gly Asn Leu Thr Pro Gln Glu Ala Ile Phe
                     935
Gln Ala Cys Leu Leu Arg Phe Arg Pro Ile Met Met Thr Thr Leu Ala
         950
                                   955
Ala Leu Phe Gly Ala Leu Pro Leu Val Leu Ser Gly Gly Asp Gly Ser
             965 970
Glu Leu Arg Gln Pro Leu Gly Ile Thr Ile Val Gly Gly Leu Val Met
                             985
Ser Gln Leu Leu Thr Leu Tyr Thr Thr Pro Val Val Tyr Leu Phe Phe
                         1000
                                            1005
Asp Arg Leu Arg Leu Arg Phe Ser Arg Lys Pro Lys Gln Thr Val Thr
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                                        1020
Glu
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Phe Gly Phe Phe Met Gln Ser Leu Asp Thr Thr Ile Val Asn Thr Ala
Leu Pro Ser Met Ala Gln Ser Leu Gly Glu Ser Pro Leu His Met His
                          40
Met Val Ile Val Ser Tyr Val Leu Thr Val Ala Val Met Leu Pro Ala
                     55
                                        60
Ser Gly Trp Leu Ala Asp Lys Val Gly Val Arg Asn Ile Phe Phe Thr
                 70
                                    75
Ala Ile Val Leu Phe Thr Leu Gly Ser Leu Phe Cys Ala Leu Ser Gly
              85
                                90
Thr Leu Asn Glu Leu Leu Ala Arg Ala Leu Gln Gly Val Gly Gly
```

```
100
                              105
Ala Met Met Val Pro Val Gly Arg Leu Thr Val Met Lys Ile Val Pro
                          120
Arg Glu Gln Tyr Met Ala Ala Met Thr Phe Val Thr Leu Pro Gly Gln
                      135
                                         140
Val Gly Pro Leu Leu Gly Pro Ala Leu Gly Gly Leu Leu Val Glu Tyr
        150
                                     155
Ala Ser Trp His Trp Ile Phe Leu Ile Asn Ile Pro Val Gly Ile Ile
                                170
Gly Ala Ile Ala Thr Leu Leu Leu Met Pro Asn Tyr Thr Met Gln Thr
          180
                             185
Arg Arg Phe Asp Leu Ser Gly Phe Leu Leu Leu Ala Val Gly Met Ala
                          200
Val Leu Thr Leu Ala Leu Asp Gly Ser Lys Gly Thr Gly Leu Ser Pro
                       215
                                         220
Leu Thr Ile Ala Gly Leu Val Ala Val Gly Val Val Ala Leu Val Leu
                   230
                                      235
Tyr Leu Leu His Ala Arg Asn Asn Asn Arg Ala Leu Phe Ser Leu Lys
              245
                                 250
Leu Phe Arg Thr Arg Thr Phe Ser Leu Gly Leu Ala Gly Ser Phe Ala
                              265
Gly Arg Ile Gly Ser Gly Met Leu Pro Phe Met Thr Pro Val Phe Leu
                         280
Gln Ile Gly Leu Gly Phe Ser Pro Phe His Ala Gly Leu Met Met Ile
                   295
                                        300
Pro Met Val Leu Gly Ser Met Gly Met Lys Arg Ile Val Val Gln Val
                   310
                                     315
Val Asn Arg Phe Gly Tyr Arg Arg Val Leu Val Ala Thr Thr Leu Gly
               325
                                  330
Leu Ser Leu Val Thr Leu Leu Phe Met Thr Thr Ala Leu Leu Gly Trp
           340
                             345
Tyr Tyr Val Leu Pro Phe Val Leu Phe Leu Gln Gly Met Val Asn Ser
                       360
                                            365
Thr Arg Phe Ser Ser Met Asn Thr Leu Thr Leu Lys Asp Leu Pro Asp
                    375
                               380
Asn Leu Ala Ser Ser Gly Asn Ser Leu Leu Ser Met Ile Met Gln Leu
                  390
                                    395
Ser Met Ser Ile Gly Val Thr Ile Ala Gly Leu Leu Gly Leu Phe
             405 410
Gly Ser Gln His Val Ser Val Asp Ser Gly Thr Thr Gln Thr Val Phe
                             425
Met Tyr Thr Trp Leu Ser Met Ala Leu Ile Ile Ala Leu Pro Ala Phe
                          440
Ile Phe Ala Arg Val Pro Asn Asp Thr His Gln Asn Val Ala Ile Ser
                       455
Arg Arg Lys Arg Ser Ala Gln
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Trp Leu Gly Ile Gln Gln Trp Arg Ala Ala Gly Ala Ile Asp Leu Lys
                              25
Ser Leu Ala Ser Thr Gln Ser Arg Arg His Leu Phe Gln Arg Ala Val
                          40
```

```
Phe Val Asn Leu Thr Asn Pro Lys Ser Ile Val Phe Leu Ala Ala Leu
       55 60
Phe Pro Gln Phe Ile Met Pro Gln Gln Pro Gln Leu Met Gln Tyr Ile
     70
                  75 80
Val Leu Gly Val Thr Thr Ile Val Val Asp Ile Ile Val Met Ile Gly
Tyr Ala Thr Leu Ala Gln Arg Ile Ala Leu Trp Ile Lys Gly Pro Lys
                     105 110
Gln Met Lys Ala Leu Asn Lys Ile Phe Gly Ser Leu Phe Met Leu Val
  115 120
Gly Ala Leu Leu Ala Ser Ala Arg His Ala
  130
                 135
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Ala Val Ala Gly Asn Ala Leu Ala Asp Glu Gly Lys Ile Thr Val Phe
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                       25
Ala Ala Ala Ser Leu Thr Asn Ala Met Gln Asp Ile Ala Thr Gln Phe
                   40
                                  45
Lys Lys Glu Lys Gly Val Asp Val Val Ser Ser Phe Ala Ser Ser Ser
               55
Thr Leu Ala Arg Gln Ile Glu Ala Gly Ala Pro Ala Asp Leu Phe Ile
Ser Ala Asp Gln Lys Trp Met Asp Tyr Ala Val Asp Lys Lys Ala Ile
        85 90 95
Asp Thr Ala Thr Arg Gln Thr Leu Leu Gly Asn Ser Leu Val Val
   100 105 110
Ala Pro Lys Ala Ser Val Gln Lys Asp Phe Thr Ile Asp Ser Lys Thr
115 120 125
Asn Trp Thr Ser Leu Leu Asn Gly Gly Arg Leu Ala Val Gly Asp Pro
 130 135
                              140
Glu His Val Pro Ala Gly Ile Tyr Ala Lys Glu Ala Leu Gln Lys Leu
145 150 155 160
Gly Ala Trp Asp Thr Leu Ser Pro Lys Leu Ala Pro Ala Glu Asp Val
           165 170 175
Arg Gly Ala Leu Ala Leu Val Glu Arg Asn Glu Ala Pro Leu Gly Ile
        180 185 190
Val Tyr Gly Ser Asp Ala Val Ala Ser Lys Gly Val Lys Val Val Ala
                    200
Thr Phe Pro Glu Asp Ser His Lys Lys Val Glu Tyr Pro Val Ala Val
                        220
  210 215
Val Glu Gly His Asn Asn Ala Thr Val Lys Ala Phe Tyr Asp Tyr Leu
225 230 235
Lys Gly Pro Gln Ala Ala Glu Ile Phe Lys Arg Tyr Gly Phe Thr Ile
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<211> 229

<212> PRT

<213> Escherichia coli

<400> 447

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Met Ile Leu Thr Asp Pro Glu Trp Gln Ala Val Leu Leu Ser Leu Lys
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Ala Trp Leu Leu Val Arg Cys Thr Phe Pro Gly Lys Ala Leu Leu Asp
                           40
Ser Val Leu His Leu Pro Leu Val Leu Pro Pro Val Val Gly Tyr
                      55
Leu Leu Val Ser Met Gly Arg Arg Gly Phe Ile Gly Glu Arg Leu
                  70
Tyr Asp Trp Phe Gly Ile Thr Phe Ala Phe Ser Trp Arg Gly Ala Val
                                  90
Leu Ala Ala Ala Val Met Ser Phe Pro Leu Met Val Arg Ala Ile Arg
                              105
          100
Leu Ala Leu Glu Gly Val Asp Val Lys Leu Glu Gln Ala Ala Arg Thr
                           120
Leu Gly Ala Gly Arg Trp Arg Val Phe Phe Thr Ile Thr Leu Pro Leu
                       135
                                          140
Thr Leu Pro Gly Ile Ile Val Gly Thr Val Leu Ala Phe Ala Arg Ser
                   150
                                      155
Leu Gly Glu Phe Gly Ala Thr Ile Thr Phe Val Ser Asn Ile Pro Gly
                                   170
              165
Glu Thr Arg Thr Ile Pro Ser Ala Met Tyr Thr Leu Ile Gln Thr Pro
                              185
Gly Gly Glu Ser Gly Ala Ala Arg Leu Cys Ile Ile Ser Ile Ala Leu
                          200
                                              205
Ala Met Ile Ser Leu Leu Ile Ser Glu Trp Leu Ala Arg Ile Ser Arg
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Glu Arg Ala Gly Arg
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                              25
Ser Gly Ala Gly Lys Thr Ser Leu Ile Asn Ala Ile Ser Gly Leu Thr
                        40
Arg Pro Gln Lys Gly Arg Ile Val Leu Asn Gly Arg Val Leu Asn Asp
Ala Glu Lys Gly Ile Cys Leu Thr Pro Glu Lys Arg Arg Val Gly Tyr
                   70
                                      75
Val Phe Gln Asp Ala Arg Leu Phe Pro His Tyr Lys Val Arg Gly Asn
                                   90
               85
Leu Arg Tyr Gly Met Ser Lys Ser Met Val Asp Gln Phe Asp Lys Leu
                               105
           100
Val Ala Leu Leu Gly Ile Glu Pro Leu Leu Asp Arg Leu Pro Gly Ser
                           120
                                              125
Leu Ser Gly Gly Glu Lys Gln Arg Val Ala Ile Gly Arg Ala Leu Leu
                      135
                                          140
Thr Ala Pro Glu Leu Leu Leu Asp Glu Pro Leu Ala Ser Leu Asp
                                    155
                150
Ile Pro Arg Lys Arg Glu Leu Leu Pro Tyr Leu Gln Arg Leu Thr Arg
               165
                                  170
Glu Ile Asn Ile Pro Met Leu Tyr Val Ser His Ser Leu Asp Glu Ile
```

```
185
Leu His Leu Ala Asp Arg Val Met Val Leu Glu Asn Gly Gln Val Lys
               200
                              205
Ala Phe Gly Ala Leu Glu Glu Val Trp Gly Ser Ser Val Met Asn Pro
          215
                                 220
Trp Leu Pro Lys Glu Gln Gln Ser Ser Ile Leu Lys Val Thr Val Leu
       230
                              235
Glu His His Pro His Tyr Ala Met Thr Ala Leu Ala Leu Gly Asp Gln
            245 . 250 255
His Leu Trp Val Asn Lys Leu Asp Glu Pro Leu Gln Ala Ala Leu Arg
        260 4 265
Ile Arg Ile Gln Ala Ser Asp Val Ser Leu Val Leu Gln Pro Pro Gln
     275 280 285
Gln Thr Ser Ile Arg Asn Val Leu Arg Ala Lys Val Val Asn Ser Tyr
 290 295
Asp Asp Asn Gly Gln Val Glu Val Glu Leu Glu Val Gly Gly Lys Thr
                310
                                315
Leu Trp Ala Arg Ile Ser Pro Trp Ala Arg Asp Glu Leu Ala Ile Lys
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Pro Gly Leu Trp Leu Tyr Ala Gln Ile Lys Ser Val Ser Ile Thr Ala
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Ala Asp Thr Lys Thr Gly Gly Phe Met Asn Arg Thr Ile Leu Val Pro
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Ile Asp Ile Ser Asp Ser Glu Leu Thr Gln Arg Val Ile Ser His Val
                      40
                                      4.5
Glu Glu Glu Ala Lys Ile Asp Asp Ala Glu Val His Phe Leu Thr Val
                 55
Ile Pro Ser Leu Pro Tyr Tyr Ala Ser Leu Gly Leu Ala Tyr Ser Ala
              70
                              75
Glu Leu Pro Ala Met Asp Asp Leu Lys Ala Glu Ala Lys Ser Gln Leu
                            90 -
Glu Glu Ile Ile Lys Lys Phe Lys Leu Pro Thr Asp Arg Val His Val
         100 105 110
His Val Glu Glu Gly Ser Pro Lys Asp Arg Ile Leu Glu Leu Ala Lys
115 120 125
Lys Ile Pro Ala His Met Ile Ile Ile Ala Ser His Arg Pro Asp Ile
 130 135
Thr Thr Tyr Leu Leu Gly Ser Asn Ala Ala Ala Val Val Arg His Ala
      150
                        155
Glu Cys Ser Val Leu Val Val Arg
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<210> 450
<211> 377
<212> PRT
<213> Escherichia coli
<400> 450
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1 5
Gly Ala Ala His Ala Ala Glu Val Tyr Asn Lys Asp Gly Asn Lys Leu
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Asp Leu Tyr Gly Lys Val Asp Gly Leu His Tyr Phe Ser Asp Asn Ser

```
Ala Lys Asp Gly Asp Gln Ser Tyr Ala Arg Leu Gly Phe Lys Gly Glu
                     55
Thr Gln Ile Asn Asp Gln Leu Thr Gly Tyr Gly Gln Trp Glu Tyr Asn
       70
Ile Gln Ala Asn Asn Thr Glu Ser Ser Lys Asn Gln Ser Trp Thr Arg
                                90
Leu Ala Phe Ala Gly Leu Lys Phe Ala Asp Tyr Gly Ser Phe Asp Tyr
                            105
Gly Arg Asn Tyr Gly Val Met Tyr Asp Ile Glu Gly Trp Thr Asp Met
               120
                                           125
Leu Pro Glu Phe Gly Gly Asp Ser Tyr Thr Asn Ala Asp Asn Phe Met
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Thr Gly Arg Ala Asn Gly Val Ala Thr Tyr Arg Asn Thr Asp Phe Phe
                  150
                                    155
Gly Leu Val Asn Gly Leu Asn Phe Ala Val Gln Tyr Gln Gly Asn Asn
              165
                                170
Glu Gly Ala Ser Asn Gly Gln Glu Gly Thr Asn Asn Gly Arg Asp Val
                             185
Arg His Glu Asn Gly Asp Gly Trp Gly Leu Ser Thr Thr Tyr Asp Leu
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Gly Met Gly Phe Ser Ala Gly Ala Ala Tyr Thr Ser Ser Asp Arg Thr
                     215
                                        220
Asn Asp Gln Val Asn His Thr Ala Ala Gly Gly Asp Lys Ala Asp Ala
                                    235
        230
Trp Thr Ala Gly Leu Lys Tyr Asp Ala Asn Asn Ile Tyr Leu Ala Thr
              245
                                 250
Met Tyr Ser Glu Thr Arg Asn Met Thr Pro Phe Gly Asp Ser Asp Tyr
                             265
Ala Val Ala Asn Lys Thr Gln Asn Phe Glu Val Thr Ala Gln Tyr Gln
            280
Phe Asp Phe Gly Leu Arg Pro Ala Val Ser Phe Leu Met Ser Lys Gly
  290 295
Arg Asp Leu His Ala Ala Gly Gly Ala Asp Asn Pro Ala Gly Val Asp
                                    315
                  310
Asp Lys Asp Leu Val Lys Tyr Ala Asp Ile Gly Ala Thr Tyr Tyr Phe
             325
                                330 335
Asn Lys Asn Met Ser Thr Tyr Val Asp Tyr Lys Ile Asn Leu Leu Asp
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Glu Asp Asp Ser Phe Tyr Ala Ala Asn Gly Ile Ser Thr Asp Asp Ile
Val Ala Leu Gly Leu Val Tyr Gln Phe
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<213> Escherichia coli
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Met Glu Phe Ile Val Glu Arg Glu Arg Leu Asp Asp Pro Phe Glu Pro
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Glu Met Ile Leu Val Gln Ser Thr Gly Met Ala Gln Trp Leu Gln Met
                          40
Thr Leu Ser Gln Lys Phe Gly Ile Ala Ala Asn Ile Asp Phe Pro Leu
```

	Ala	Ser	Phe	Ile		Asp	Met	Phe	Val		Val	Leu	Pro	Glu	
65 Pro	Lys	Glu	Ser	Ala	70 Phe	Asn	Lys	Gln	Ser	75 Met	Ser	Trp	Lys	Leu	80 Met
Thr	ī.en	T.eu	Pro	85 Gln	Len	ĭ.en	Glu	Ara	90 Glu	Asp	Phe	Thr	Len	95 Len	Ara
			100					105		_			110		
His	Tyr	Leu 115	Thr	Asp	Asp	Ser	Asp 120	Lys	Arg	Lys	Leu	Phe 125	Gln	Leu	Ser
Ser	Lys 130	Ala	Ala	Asp	Leu	Phe 135	Asp	Gln	Tyr	Leu	Val 140	Tyr	Arg	Pro	Asp
Trp 145		Ala	Gln	Trp	Glu 150	Thr	Gly	His	Leu	Val 155	Glu	Gly	Leu		Glu 160
	Gln	Ala	Trp	Gln 165		Pro	Leu	Trp	Lys 170		Leu	Val	Glu		
His	Gln	Leu	Gly 180	Gln	Pro	Arg	Trp	His 185		Ala	Asn	Leu	Tyr 190		Arg
Phe	Ile	Glu 195		Leu	Glu	Ser	Ala 200		Thr	Cys	Pro	Pro 205		Leu	Pro
Ser	_		Phe	Ile	Cys			Ser	Ala	Leu			Val	Tyr	Leu
Gln	210 Ala	Leu	Gln	Ala	Leu	215 Gly	Lys	His	Ile	Glu	220 Ile	His	Leu	Leu	Phe
225		_	_	_	230		1				٠.	·	_	<u>:</u> .	240
				Arg 245					250				٠	255	-
Leu	Ala	Lys	Leu 260	Leu	Thr	Arg	Gln	Arg 265	Arg	His	Ser	Phe	Glu 270	Asp	Arg
Glu	Leu	Pro 275	Leu	Phe	Arg	Asp	Ser 280	Glu	Asn	Ala	Gly	Gln 285	Leu	Phe	Asn
Ser	Asp 290	Gly	Glu	Gln	Asp	Val 295	Gly	Asn	Pro	Leu	Leu 300	Ala	Ser	Trp	Gly
Lys 305	Leu	Gly	Arg	Asp	Tyr 310	Ile	Tyr	Leu	Leu	Ser 315	Asp	Leu	Glu	Ser	Ser 320
Gln	Glu	Leu	Asp	Ala 325	Phe	Val	Asp	Val	Thr 330	Pro	Asp	Asn	Leu	Leu 335	His
Asn	Ile	Gln	Ser 340	Asp	Ile	Leu	Glu	Leu 345	Glu	Asn	Arg	Ala	Val 350	Ala	Gly
Val	Asn	Ile 355		Glu	Phe	Ser	Arg 360	Ser	qaA	Asn	Lys	Arg 365	Pro	Leu	Asp
Pro	Leu 370		Ser	Ser	Ile	Thr 375		His	Val	Суз	His 380		Pro	Gln	Arg
Glu 385		Glu	Val	Leu	His 390		Arg	Leu	Leu	Ala 395		Leu	Glu	Glu	Asp 400
	Thr	Leu	Thr	Pro		Asp				Met	Val	Ala	Asp	Ile	
C	M	Cam	Desc	405		CIn	ת 1 ת	Wa 1	410	C1	802	ת ז ת		415	
			420	Phe -				425					430		
•	Tyr	Leu 435	Pro	Tyr	Ala	TTE	Ser	Asp	Arg	Arg	Ата	Arg	GIN	Ser	HIS
							440					445			
	450	Leu		Ala		455	Ser			Ser	460	Pro	_		_
	450	Leu		Ala Asp	Val	455	Ser			Ser	460	Pro	_		Ala
465	450 Val	Leu Ser	Glu	Asp Ile	Val 470	455 Leu	Ser Ala	Leu	Leu Leu	Ser Asp 475	460 Val	Pro Pro	Val	Leu Gln	Ala 480
465 Ala	450 Val Arg	Leu Ser Phe	Glu Asp Ser	Asp Ile 485	Val 470 Thr	455 Leu Glu	Ser Ala Glu	Leu Gly Gly	Leu Leu 490	Ser Asp 475 Arg	460 Val Tyr	Pro Pro Leu	Val Arg Asn	Leu Gln 495	Ala 480
465 Ala Val	450 Val Arg Asn	Leu Ser Phe Glu Glu	Glu Asp Ser 500	Asp Ile 485	Val 470 Thr	455 Leu Glu Arg	Ser Ala Glu Trp Gly	Leu Gly Gly 505	Leu Leu 490 Ile	Ser Asp 475 Arg Asp	460 Val Tyr Asp	Pro Pro Leu Asp Arg	Val Arg Asn 510	Leu Gln 495 Val	Ala 480 Trp Arg
465 Ala Val Glu	450 Val Arg Asn Leu	Leu Ser Phe Glu Glu 515	Glu Asp Ser 500 Leu	Asp Ile 485 Gly	Val 470 Thr Ile Ala	455 Leu Glu Arg Thr	Ser Ala Glu Trp Gly 520	Leu Gly Gly 505 Gln	Leu Leu 490 Ile His	Ser Asp 475 Arg Asp	460 Val Tyr Asp	Pro Pro Leu Asp Arg 525	Val Arg Asn 510 Phe	Leu Gln 495 Val Gly	Ala 480 Trp Arg Leu

Gln 545	Ser	Val	Leu	Pro	Tyr 550	Asp	Glu	Ser	Ser	Gly 555	Leu	Ile	Ala	Glu	Leu 560
Val	Gly	His	Leu	Ala 565	Ser	Leu	Leu	Met	Gln 570		Asn	Ile	Trp	Arg 575	
Gly	Leu	Ala	Gln 580	Glu	Arg	Pro	Leu	Glu 585	Glu	Trp	Leu	Pro	Val 590	Cys	Arg
Asp	Met	Leu 595	Asn	Ala	Phe	Phe	Leu 600	Pro	Asp	Ala	Glu	Thr 605	Glu	Ala	Ala
Met	Thr 610	Leu	Ile	Glu	Gln	Gln 615	Trp	Gln	Ala	Ile	Ile 620	Ala	Glu	Gly	Leu
625			Tyr	_	630					635			_	-	640
			Arg	645	-			_	650			_		655	
_			Asn 660					665			_		670		
		675	Cys				680					685		_	
	690		Leu			695					700		-	_	_
705			Arg		710				_	715					720
			Gln	725	_		_		730	_		_	•	735	
	_		Ser 740					745					750		
		755	Gly				760				_	765			
_	770		Ser			775					780				
785			Pro Arg		790					795				_	800
	_		Phe	805					810				_	815	
			820 Thr					825					830		
		835	Arg				840					845			
	850		Glu			855					860	-			
865					870					875			_		880
				885					890		_	_		895	-
		_	Arg 900					905	_			_	910		
_		915	Phe	_			920					925			
	930		Ile			935					940				
945		_	Asn	_	950					955					960
	_		Leu	965	_				970					975	
_			Leu 980					985					990	-	_
	_	995	Ser	_			1000	<u></u>				1009	5		
Pro	Pro 1010	_	Ala	Ala	Glu	Gln 101		Leu	His	Tyr	Leu 1020	_	Gln	Leu	Ile

Glu Gly Tyr Arg Glu Gly Met Ser Ala Pro Leu Leu Val Leu Pro Glu 1035 1030 Ser Gly Gly Ala Trp Leu Lys Thr Cys Tyr Asp Ala Gln Asn Asp Ala 1050 1045 Met Leu Asp Asp Asp Ser Thr Leu Gln Lys Ala Arg Thr Lys Phe Leu 1060 1065 1070 Gln Ala Tyr Glu Gly Asn Met Met Val Arg Gly Glu Gly Asp Asp Ile 1080 1085 1075 Trp Tyr Gln Arg Leu Trp Arg Gln Leu Thr Pro Glu Thr Met Glu Ala 1095 1100 Ile Val Glu Gln Ser Gln Arg Phe Leu Leu Pro Leu Phe Arg Phe Asn 1110 Gln Ser <210> 452 <211> 107 <212> PRT <213> Escherichia coli <400> 452 Met Ser Ala Ser Leu Lys Asn Gln Gln Gly Phe Ser Leu Pro Glu Val 5 10 15 Met Leu Ala Met Val Leu Met Val Met Ile Val Thr Ala Leu Ser Gly 20 25 Phe Gln Arg Thr Leu Met Asn Ser Leu Ala Ser Arg Asn Gln Tyr Gln 40 Gln Leu Trp Arg His Gly Trp Gln Gln Thr Gln Leu Arg Ala Ile Ser 55 Pro Pro Ala Asn Trp Gln Val Asn Arg Met Gln Thr Ser Gln Ala Gly 70 75 Cys Val Ser Ile Ser Val Thr Leu Val Ser Pro Gly Gly Arg Glu Gly . 90 85 Glu Met Thr Arg Leu His Cys Pro Asn Arg Gln 100 <210> 453 <211> 121 <212> PRT <213> Escherichia coli <400> 453 Met Leu Leu Val Leu Gly Ser Leu Leu Leu Gln Gly Met Ser Gln Gln 10 Asp Arg Ser Phe Ala Ser Arg Val Ser Met Glu Ser Gln Ser Leu Arg 20 25 Arg Gln Ala Ile Val Gln Ser Ala Leu Ala Trp Gly Lys Met His Cys 45 40 Trp Gln Thr Gln Pro Ala Val Gln Cys Ser Gln Tyr Ala Glu Thr Asp 55 60 Ala Gin Val Cys Leu Arg Leu Leu Ala Asp Asn Glu Ala Leu Leu Ile 75 Ala Gly Tyr Glu Gly Val Ser Leu Trp Arg Thr Gly Glu Val Ile Asp 90 Gly Asn Ile Val Phe Ser Pro Arg Gly Trp Ser Asp Phe Cys Pro Leu

<210> 454

115

100

Lys Glu Arg Ala Leu Cys Gln Leu Pro

105

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Met Ala Ile Ser Ser Val Leu Leu Gly Ala Ala Arg Phe Leu Pro
                            25
Ala Leu Gln Arg Glu Ser Leu Thr Ser Thr Arg Lys Leu Ala Leu Glu
                      40
                                           45
Asp Glu Ile Trp Leu Arg Val Phe Thr Val Ala Lys His Leu Gln Arg
                     55
                                       60
Ala Gly Tyr Cys His Gly Ile Cys Thr Gly Glu Gly Leu Glu Ile Val
Gly Gln Gly Asp Cys Val Ile Val Gln Trp Asp Ala Asn Ser Asn Gly
             85
                                90
Ile Trp Asp Arg Glu Pro Val Lys Glu Ser Asp Gln Ile Gly Phe Arg
           100
                             105
                                               110
Leu Lys Glu His Val Leu Glu Thr Leu Arg Gly Ala Thr Ser Cys Glu
                         120
      115
Gly Lys Gly Trp Asp Lys Val Thr Asn Pro Asp Ala Ile Ile Ile Asp
                    135
                                       140
Thr Phe Gln Val Val Arg Gln Asp Val Ser Gly Phe Ser Pro Val Leu
        150 155 160
Thr Val Asn Met Arg Ala Ala Ser Lys Ser Glu Pro Gln Thr Val Val
            165
                                170
Asn Ala Ser Tyr Ser Val Thr Gly Phe Asn Leu
                             185
          180
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Leu Ile Leu Val Met Leu Ser Ala Ser Gly Leu Tyr Gly Trp Gln Tyr
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                          25
Trp Gln Gln Ser Gln Arg Leu Trp Gln Thr Ala Ser Gln Ala Arg Asp
                         40
Tyr Leu Leu Tyr Leu Arg Glu Asp Ala Asn Trp His Asn Arg Asp His
                     55
                                        60
Ser Ile Ser Val Ile Arg Glu Gly Thr Leu Trp Cys Leu Val Ser Ser
                 70
                                  75
Ala Ala Gly Ala Asn Thr Cys His Gly Ser Ser Pro Leu Val Phe Val
                                 90
Pro Arg Trp Pro Glu Val Glu Met Ser Asp Leu Thr Pro Ser Leu Ala
                             105
Phe Phe Gly Leu Arg Asn Thr Ala Trp Ala Gly His Ile Arg Phe Lys
                         120
                                            125
Asn Ser Thr Gly Glu Trp Trp Leu Val Val Ser Pro Trp Gly Arg Leu
                     135
                                       140
Arg Leu Cys Gln Gln Gly Glu Thr Glu Gly Cys Leu
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<210> 456
<211> 711
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#### <213> Escherichia coli

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460

455

```
Glu Ser Arg Val Ser Ala Ser Leu Arg Ser Ala Ile Gln Lys Ser Gly
                  470
                                      475
Met Val Leu Leu Asp Asp Phe Gly Asp Ile Val Leu Lys Thr Ala Asp
                                  490
              485
Leu Cys Ser Ala Lys Asp Asp Cys Val Arg Leu Lys Asn Ala Leu Val
                              505
Asn Leu Gly Asn Ser Lys Asp Trp Asp Ala Leu Val Lys Arg Ala Asn
                          520
Ala Gly Lys Leu Asp Gly Val Asn Val Leu Leu Arg Pro Val Ser Ala
                     535
                                         540
Glu Ser Leu Asp Asn Leu Val Ala Thr Ser Thr Ala Pro Phe Ile Thr
          550
                           555
His Glu Thr Ala Arg Ala Ala Gln Ser Leu Asn Ser Pro Ala Pro Gly
              565
                                  570
Gly Phe Leu Ile Val Ser Asp Glu Gly Ser Asp Phe Val Asp Gln Pro
                               585
Trp Pro Ser Ala Ser Leu Tyr Asp Tyr Pro Pro Gln Glu Gln Trp Asn
                          600
Ala Phe Gln Lys Leu Ala Gln Met Leu Met His Thr Pro Phe Asn Ala
                      615
                                          620
Glu Gly Ile Val Thr Lys Ile Phe Thr Asp Ala Asn Gly Thr Gln His
                  630
                                     635
Ile Gly Leu His Pro Ile Pro Asp Arg Ser Gly Leu Trp Arg Tyr Leu
              645
                                  650
Ser Thr Thr Leu Leu Leu Leu Thr Met Leu Gly Ser Ala Ile Tyr Asn
                              665
Gly Val Gln Ala Trp Arg Arg Tyr Gln Arg His Arg Thr Arg Met Met
                          680
Glu Ile Gln Ala Tyr Tyr Glu Ser Cys Leu Asn Pro Gln Leu Ile Thr
             695
Pro Ser Glu Ser Leu Ile Glu
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<211> 237
<212> PRT
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<400> 457
Met Leu Pro Cys Arg Ala Asn Cys Phe Thr Leu Glu Ile Ser Leu Met
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His Ile Asn Ile Ala Trp Gln Asp Val Asp Thr Val Leu Leu Asp Met
Asp Gly Thr Leu Leu Asp Leu Ala Phe Asp Asn Tyr Phe Trp Gln Lys
                           40
Leu Val Pro Glu Thr Trp Gly Ala Lys Asn Gly Val Thr Pro Gln Glu
                       55
Ala Met Glu Tyr Met Arg Gln Gln Tyr His Asp Val Gln His Thr Leu
Asn Trp Tyr Cys Leu Asp Tyr Trp Ser Glu Gln Leu Gly Leu Asp Ile
                                   90
Cys Ala Met Thr Thr Glu Met Gly Pro Arg Ala Val Leu Arg Glu Asp
          100
                              105
Thr Ile Pro Phe Leu Glu Ala Leu Lys Ala Ser Gly Lys Gln Arg Ile
                          120
Leu Leu Thr Asn Ala His Pro His Asn Leu Ala Val Lys Leu Glu His
                       135
                                          140
Thr Gly Leu Asp Ala His Leu Asp Leu Leu Leu Ser Thr His Thr Phe
                   150
                                      155
```

```
Gly Tyr Pro Lys Glu Asp Gln Arg Leu Trp His Ala Val Ala Glu Ala
              165 . 170
Thr Gly Leu Lys Ala Glu Arg Thr Leu Phe Ile Asp Asp Ser Glu Ala
                            185
          180
Ile Leu Asp Ala Ala Ala Gln Phe Gly Ile Arg Tyr Cys Leu Gly Val
                          200
                                           205
Thr Asn Pro Asp Ser Gly Ile Ala Glu Lys Gln Tyr Gln Arg His Pro
                       215
Ser Leu Asn Asp Tyr Arg Arg Leu Ile Pro Ser Leu Met
                   230
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<211> 133
<212> PRT
<213> Escherichia coli
<400> 458
Met Lys Glu Lys Pro Ala Val Glu Val Arg Leu Asp Lys Trp Leu Trp
                                  10
Ala Ala Arg Phe Tyr Lys Thr Arg Ala Leu Ala Arg Glu Met Ile Glu
           20
                               25
Gly Gly Lys Val His Tyr Asn Gly Gln Arg Ser Lys Pro Ser Lys Ile
                           40
Val Glu Leu Asn Ala Thr Leu Thr Leu Arg Gln Gly Asn Asp Glu Arg
Thr Val Ile Val Lys Ala Ile Thr Glu Gln Arg Arg Pro Ala Ser Glu
                  70
Ala Ala Leu Leu Tyr Glu Glu Thr Ala Glu Ser Val Glu Lys Arg Glu
                                  90
Lys Met Ala Leu Ala Arg Lys Leu Asn Ala Leu Thr Met Pro His Pro
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Asp Arg Arg Pro Asp Lys Lys Glu Arg Arg Asp Leu Leu Arg Phe Lys
                          120
His Gly Asp Ser Glu
  130
<210> 459
<211> 294
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<213> Escherichia coli
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Met Ile Met Pro Gln His Asp Gln Leu His Arg Tyr Leu Phe Glu Asn
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Phe Ala Val Arg Gly Glu Leu Val Thr Val Ser Glu Thr Leu Gln Gln
                               25
Ile Leu Glu Asn His Asp Tyr Pro Gln Pro Val Lys Asn Val Leu Ala
                           40
Glu Leu Leu Val Ala Thr Ser Leu Leu Thr Ala Thr Leu Lys Phe Asp
                       55
                                           60
Gly Asp Ile Thr Val Gln Leu Gln Gly Asp Gly Pro Met Asn Leu Ala
                                       75
                   70
Val Ile Asn Gly Asn Asn Asn Gln Gln Met Arg Gly Val Ala Arg Val
                                   90
               85
Gln Gly Glu Ile Pro Glu Asn Ala Asp Leu Lys Thr Leu Val Gly Asn
           100
                               105
Gly Tyr Val Val Ile Thr Ile Thr Pro Ser Glu Gly Glu Arg Tyr Gln
                           120
                                               125
Gly Val Val Gly Leu Glu Gly Asp Thr Leu Ala Ala Cys Leu Glu Asp
                       135
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Tyr Phe Met Arg Ser Glu Gln Leu Pro Thr Arg Leu Phe Ile Arg Thr
                  150
                                    155
Gly Asp Val Asp Gly Lys Pro Ala Ala Gly Gly Met Leu Leu Gln Val
                                   170
               165
Met Pro Ala Gln Asn Ala Gln Gln Asp Asp Phe Asp His Leu Ala Thr
                               185
           180
Leu Thr Glu Thr Ile Lys Thr Glu Glu Leu Leu Thr Leu Pro Ala Asn
                           200
Glu Val Leu Trp Arg Leu Tyr His Glu Glu Glu Val Thr Val Tyr Asp
                   215
                                          220
Pro Gln Asp Val Glu Phe Lys Cys Thr Cys Ser Arg Glu Arg Cys Ala
                  230
                                      235
Asp Ala Leu Lys Thr Leu Pro Asp Glu Glu Val Asp Ser Ile Leu Ala
                                  250
Glu Asp Gly Glu Ile Asp Met His Cys Asp Tyr Cys Gly Asn His Tyr
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Leu Phe Asn Ala Met Asp Ile Ala Glu Ile Arg Asn Asn Ala Ser Pro
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Ala Asp Pro Gln Val His
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Leu Ile His Trp Val Val Phe Gly Val Cys Ile Tyr Val Ala His Thr
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Asn Gln Ala Leu Ala Asn Phe Ala Gly Phe Val Val Ala Val Ser Phe
Ser Phe Phe Ala Asn Ala Lys Phe Thr Phe Lys Ala Ser Thr Thr Thr
Met Arg Tyr Met Leu Tyr Val Gly Phe Met Gly Thr Leu Ser Ala Thr
                70
Val Gly Trp Ala Ala Asp Arg Cys Ala Leu Pro Pro Met Ile Thr Leu
              85
Val Thr Phe Ser Ala Ile Ser Leu Val Cys Gly Phe Val Tyr Ser Lys
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Phe Ile Val Phe Arg Asp Ala Lys
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1
Pro Ile Phe Tyr Lys Thr Val Arg Glu Phe Glu Glu Leu Lys Ser Tyr
                               25
Glu Val Glu Ile Val Phe Ile Asn Asp Gly Ser Lys Asp Ala Thr Glu
                           40
Ser Ile Ile Asn Ala Leu Ala Val Ser Asp Pro Leu Val Val Pro Leu
                       55
                                          60
Ser Phe Thr Arg Asn Phe Gly Lys Glu Pro Ala Leu Phe Ala Gly Leu
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Asp His Ala Thr Gly Asp Ala Ile Ile Pro Ile Asp Val Asp Leu Gln
             85
                                  90
Asp Pro Ile Glu Val Ile Pro His Leu Ile Glu Lys Trp Gln Ala Gly
       100
                              105
Ala Asp Met Val Leu Ala Lys Arg Ser Asp Arg Ser Thr Asp Gly Arg
                          120
Leu Lys Arg Lys Thr Ala Glu Trp Phe Tyr Lys Leu His Asn Lys Ile
                      135
                                        140
Ser Asn Pro Lys Ile Glu Glu Asn Val Gly Asp Phe Arg Leu Met Ser
                                    155
                  150
Arg Asp Val Val Glu Asn Ile Lys Leu Met Pro Glu Arg Asn Leu Phe
                                 170
Met Lys Gly Ile Leu Ser Trp Val Gly Gly Lys Thr Asp Ile Val Glu
                             185
Tyr Val Arg Ala Glu Arg Ile Ala Gly Asp Thr Lys Phe Asn Gly Trp
                         200
Lys Leu Trp Asn Leu Ala Leu Glu Gly Ile Thr Ser Phe Ser Thr Phe
                                        220
                     215
Pro Leu Arg Ile Trp Thr Tyr Ile Gly Leu Val Val Ala Ser Val Ala
                  230
                                     235
Phe Ile Tyr Gly Ala Trp Met Ile Leu Asp Thr Ile Ile Phe Gly Asn
                                  250
Ala Val Arq Gly Tyr Pro Ser Leu Leu Val Ser Ile Leu Phe Leu Gly
                           265
                                          270
           260
Gly Ile Gln Met Ile Gly Ile Gly Val Leu Gly Glu Tyr Ile Gly Arg
                       280
Thr Tyr Ile Glu Thr Lys Lys Arg Pro Lys Tyr Ile Ile Lys Arg Val
Lys Lys
305
<210> 462
<211> 443
<212> PRT
<213> Escherichia coli
<400> 462
Met Asn Lys Ala Ile Lys Val Ser Leu Tyr Ile Ser Phe Val Leu Ile
                                  10
Ile Cys Ala Leu Ser Lys Asn Ile Met Met Leu Asn Thr Ser Asp Phe
                              25
Gly Arg Ala Ile Lys Pro Leu Ile Glu Asp Ile Pro Ala Phe Thr Tyr
Asp Leu Pro Leu Leu Tyr Lys Leu Lys Gly His Ile Asp Ser Ile Asp
                     55
Ser Tyr Glu Tyr Ile Ser Ser Tyr Ser Tyr Ile Leu Tyr Thr Tyr Val
                  70
                                     75
Leu Phe Ile Ser Ile Phe Thr Glu Tyr Leu Asp Ala Arg Val Leu Ser
                                 90
              8.5
Leu Phe Leu Lys Val Ile Tyr Ile Tyr Ser Leu Tyr Ala Ile Phe Thr
                             105
                                                110
          100
Ser Tyr Ile Lys Thr Glu Arg Tyr Val Thr Leu Phe Thr Phe Phe Ile
                                            125
            120
Leu Ala Phe Leu Met Cys Ser Ser Ser Thr Leu Ser Met Phe Ala Ser
                      135
                                         140
Phe Tyr Gln Glu Gln Ile Val Ile Ile Phe Leu Pro Phe Leu Val Tyr
                 150 155
Ser Leu Thr Cys Lys Asn Asn Lys Ser Met Leu Leu Leu Phe Phe Ser
              165 170
Leu Leu Ile Ile Ser Thr Ala Lys Asn Gln Phe Ile Leu Thr Pro Leu
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180
                            185
Ile Val Tyr Ser Tyr Tyr Ile Phe Phe Asp Arg His Lys Leu Ile Ile
                        200
                                         205
    195
Lys Ser Val Ile Cys Val Val Cys Leu Leu Ala Ser Ile Phe Ala Ile
                                    220
                  215
Ser Tyr Ser Lys Gly Val Val Glu Leu Asn Lys Tyr His Ala Thr Tyr
       230
                                 235
Phe Gly Ser Tyr Leu Tyr Met Lys Asn Asn Gly Tyr Lys Met Pro Ser
                     250
Tyr Val Asp Asp Lys Cys Val Gly Leu Asp Ala Trp Gly Asn Lys Phe
                 265
Asp Ile Ser Phe Gly Ala Thr Pro Thr Glu Val Gly Thr Glu Cys Phe
     275 280
Glu Ser His Lys Asp Glu Thr Phe Ser Asn Ala Leu Phe Leu Leu Val
                                       300
                    295
Ser Lys Pro Ser Thr Ile Phe Lys Leu Pro Phe Asp Asp Gly Val Met
                  310
                                    315
Ser Gln Tyr Lys Glu Asn Tyr Phe His Val Tyr Lys Lys Leu His Val
                  330
              325
Ile Tyr Gly Glu Ser Asn Ile Leu Thr Thr Ile Thr Asn Ile Lys Asp
                            345
          340
Asn Ile Phe Lys Asn Ile Arg Phe Ile Ser Leu Leu Leu Phe Phe Ile
                       360
                                365
Ala Ser Ile Phe Ile Arg Asn Asn Lys Ile Lys Ala Ser Leu Phe Val
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#### **PCT**

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- (75) Inventors/Applicants (for US only): FORSYTH, R., Allyn [US/US]; 1135 Bcryl Street. San Diego, CA 92116 (US). OHLSEN, Kari [US/US]; 3560 Vista de La Orilla, San Diego, CA 92117 (US). ZYSKIND, Judith [US/US]; 8415 La Jolla Scenic Drive, La Jolla, CA 92037 (US).
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- (81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

#### Published:

- with international search report
- (88) Date of publication of the international search report: 10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A3

(54) Title: GENES ESSENTIAL FOR MICROBIAL PROLIFERATION

(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms as well as to screen for antimicrobial agents.

### INTERNATIONAL SEARCH REPORT

Intern Tal Application No PCT/US 00/30950

			0/30330
A. CLASS IPC 7	FICATION OF SUBJECT MATTER C12N15/31 C12N15/11 C12N1	.5/10 C07K14/245	
According t	to International Patent Classification (IPC) or to both national clas	sification and IPC	
	SEARCHED	<u></u>	·
Minimum di IPC 7	ocumentation searched (classification system followed by classi C12N C07K	ication symbols)	
Documenta	tion searched other than minimum documentation to the extent t	nat such documents are included in the fields s	earched
	data base consulted during the international search (name of data		)
SEQUEN	ICE SEARCH, EPO-Internal, WPI Data	, PAU, BIUSIS	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.
X	DATABASE EM_PRO [Online] EMBL; 29 January 1997 (1997-01 BLATTNER ET AL.: "Escherichia MG1655 section 101 of 400 of t	5,10,13, 14, 18-21, 124	
	genome" retrieved from EBI, accession Database accession no. AE00021 XP002181472 the whole document		
Y X	-& DATABASE SWALL [Online] 15 July 1998 (1998-07-15) BLATTNER ET AL.: "Hypothetical protein YCFS precursor" retrieved from EBI, accession no. YCFS ECOLI		1-131 5,10,13, 14, 18-21, 124
	Database accession no. P75954 XP002181473 the whole document		
X Funt	ner documents are listed in the continuation of box C.	Patent family members are listed in	annex.
<u> </u>	tegories of cited documents :		
"A" docume consid	ent defining the general state of the art which is not lered to be of particular relevance	"T" later document published after the inter or priority date and not in conflict with to cited to understand the principle or the invention	he application but
filing d	tocument but published on or after the international later which may throw doubts on priority claim(s) or is cited to establish the publication date of another	"X" document of particular relevance; the cl cannot be considered novel or cannot in involve an inventive step when the doc "Y" document of particular relevance; the cl	be considered to ument is taken alone
citation "O" docume other r	n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means	cannot be considered to involve an inv document is combined with one or mor ments, such combination being obviou in the art.	entive step when the e other such docu-
	ent published prior to the international filing date but an the priority date claimed	"&" document member of the same patent for	amily
	actual completion of the international search  5 November 2001	Date of mailing of the international sear	ch report
Name and n	nailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk Tal (+31-70) 340-3400 Tv 31 651 eon al	Authorized officer	
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## INTERNATIONAL SEARCH REPORT

Interm nat Application No
PCT/US 00/30950

X -& DATABASE EM PRO [Online] EMBL; 29 January 1997 (1997-01-29) BLATTNER ET AL.: "Escherichia coli KI2 MG1655 section 305 of 400 of the complete genome" retrieved from EBI, accession no. ECAE415 Database accession no. AE000415 XP002181474 the whole document -& DATABASE SWALL [Online] 1 November 1995 (1995-11-01) BLATTNER ET AL.: "Hypothetical 79.5 kDa protein in NRCA-PCKA intergenic region (0711)" retrieved from EBI, accession no. YRFF ECOLI Database accession no. P45800 XP002181475 the whole document -& BLATTNER ET AL.: "The complete genome sequence of Escherichia coli K-12" SCIENCE, vol. 277, 5 September 1997 (1997-09-05), pages 1453-1462, FIFURES, XP002923023 the whole document  Y WO 99 02673 A (DUGOURD DOMINIQUE ;WRIGHT JIM A (CA); YOUNG AIPING H (CA); GENESEN) 21 January 1999 (1999-01-21) page 7, line 25 -page 9, line 30; examples 2-6  X DATABASE EM PRO [Online] EMBL; 31 October 1996 (1996-10-31) OSHIMA ET AL.: "Escherichia coli genomic DNA (25.2-25.6 min)" retrieved from EBI, accession no. ECD747 Database accession no. D90747 XP002181476 the whole document -& DNA RES. vol. 3, 1996, pages 137-155, XP001040039  X DATABASE EM PRO [Online] EMBL; 30 December 1994 (1994-12-30)  A DATABASE EM PRO [Online] EMBL; 30 December 1994 (1994-12-30)	) 	8/3 <del>8958</del>	PCT/US 0		
A DATABASE EM PRO [Online]   14.	·				
EMBL; 29 January 1997 (1997-01-29) BLATTNER ET AL.: "Escherichia coli K12 MG1655 section 305 of 400 of the complete genome" retrieved from EBI, accession no. ECAE415 Database accession no. AE000415 XP002181474 the whole document -& DATABASE SWALL [Online] 1 November 1995 (1995-11-01) BLATTNER ET AL.: "Hypothetical 79.5 kDa protein in NRCA-PCKA intergenic region (0711)" retrieved from EBI, accession no. YRFF ECOLI Database accession no. P45800 XP002181475 the whole document -& BLATTNER ET AL.: "The complete genome sequence of Escherichia coli K-12" SCIENCE, vol. 277, 5 September 1997 (1997-09-05), pages 1453-1462, FIFURES, XP002923023 the whole document -W0 99 02673 A (DUGOURD DOMINIQUE ;WRIGHT JIM A (CA); YOUNG AIPING H (CA); GENESEN) 21 January 1999 (1999-01-21) page 7, line 25 -page 9, line 30; examples 2-6  DATABASE EM PRO [Online] EMBL; 31 October 1996 (1996-10-31) OSHIMA ET AL.: "Escherichia coli genomic DNA (25.2-25.6 min)" retrieved from EBI, accession no. ECD747 Database accession no. D90747 XP002181476 the whole document -& DNA RES., vol. 3, 1996, pages 137-155, XP001040039  (DATABASE EM PRO [Online] EMBL; 30 December 1994 (1994-12-30) PLUNKETT, G: "Escherichia coli K-12 chromosomal region from 67.4 to 76 minutes" retrieved from EBI, accession no. ECUW67 Database accession no. U18997 XP002181477  Tetrieved from EBI, accession no. ECUW67 Database accession no. U18997 XP002181477	claim No.	Relevant to clair		Citation of document, with indication, where appropriate, of the relevant passages	Category *
the whole document -& DATABASE EMPRO [Online] 1 November 1995 (1995-11-01) 14 BLATTNER ET AL.: "Hypothetical 79.5 kDa protein in MRCA-PCKA intergenic region (0711)" retrieved from EBI, accession no. YRFF ECOLI Database accession no. P45800 XP002181475 the whole document -& BLATTNER ET AL.: "The complete genome sequence of Escherichia coli K-12" SCIENCE, vol. 277, 5 September 1997 (1997-09-05), pages 1453-1462, FIFURES, XP002923023 the whole document  WO 99 02673 A (DUGOURD DOMINIQUE ;WRIGHT JIM A (CA); YOUNG AIPING H (CA); GENESEN) 21 January 1999 (1999-01-21) page 7, line 25 -page 9, line 30; examples 2-6  DATABASE EM PRO [Online] EMBL; 31 October 1996 (1996-10-31)	-21,	5,10, 14, 18-21 124		EMBL; 29 January 1997 (1997-01-29) BLATTNER ET AL.: "Escherichia coli K12 MG1655 section 305 of 400 of the complete genome" retrieved from EBI, accession no. ECAE415 Database accession no. AE000415	X
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Intern rai Application No PCT/US 00/30950

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C.(Continu	etion) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate. of the relevant passages	Relevant to claim No.
A	POST L E ET AL: "NUCLEOTIDE SEQUENCE OF THE RIBOSOMAL PROTEIN GENE CLUSTER ADJACENT TO THE GENE FOR RNA POLYMERASE SUBUNIT BETA IN ESCHERICHIA COLI" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, US, NEW YORK, NY, vol. 76, no. 4, 1 April 1979 (1979-04-01), pages 1697-1701, XP000574791 abstract	1
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Internal Application No PCT/US 00/30950

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C.(Continue	tion) DOCUMENTS CONSIDERED TO BE RELEVANT		
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E	WO 01 48209 A (OHLSEN KARI L ;FORSYTH R ALLYN (US); ELITRA PHARMACEUTICALS INC (U) 5 July 2001 (2001-07-05) page 3 -page 14 seq id nos 274, 467	1-131	
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## INTERNATIONAL SEARCH REPORT

In ational application No. PCT/US 00/30950

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  See FURTHER INFORMATION sheet PCT/ISA/210
2. X Claims Nos.:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As a result of the prior review under R. 40.2(e) PCT, part of the additional fees are to be refunded.
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. X As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-131 (Seq Id Nos 1, 116, 128, 285, 299, 456)
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  X The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 129-131 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Present claims 36, 44, 57, 95, 98, 109 and 117 relate to a compound defined by reference to a desirable characteristic or property, namely being identifiable by using the method of claims 28, 38, 45, 84, 96, 99, or 110, respectively. Present claims 125 and 126 relate to a compound defined by reference to a desirable characteristic or property, namely interacting with a gene or gene product or a polypeptide whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOS 1-127.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the sequences of claims 1, 9 and 19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 12-14, 45-124, 129-130 all partially

Invention 1:

A purified or isolated nucleic acid sequence, consisting of Seq Id No 1, a vector comprising said sequence, a host cell containing said vector, and their uses.

2. Claims: 1-8, 12-14, 45-124, 129-130 all partially

Inventions 2 to 127:

Idem as invention 1, but for Seq Id Nos 2-127, respectively.

3. Claims: 9-11, 15-44, 125-128 all partially

Invention 128:

A purified or isolated nucleic acid sequence consisting of Seq Id No 128, a vector comprising said sequence, a host cell containing said vector, a polypeptide encoded by said nucleic acid sequence and having Seq Id No 299, and an antibody binding said polypeptide, and their uses.

4. Claims: 9-11, 15-44, 125-128 all partially

Inventions 129 to 298:

Idem as invention 128, but for nucleic acid Seq Id Nos 129-298 and corresponding polypeptide Seq Id Nos 300-469, respectively.

## INTERNATIONAL SEARCH REPORT

information on patent family members

Intern ral Application No PCT/US 00/30950

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